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(54) **TRANSDERMAL OPTOGENETIC PERIPHERAL NERVE STIMULATION**

TRANSDERMALE OPTOGENETISCHE PERIPHERE NERVENSTIMULATION

STIMULATION OPTOGÉNÉTIQUE TRANSDERMIQUE DU NERF PÉRIPHÉRIQUE

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Description

RELATED APPLICATIONS

5 **[0001]** This application claims the benefit of U.S. Provisional Application No. 62/415,817, filed on November 1, 2016.

BACKGROUND OF THE INVENTION

10 **[0002]** Optogenetic techniques have recently been applied to peripheral nerves as a scientific tool with the translatable goal of alleviating a variety of disorders, including chronic pain¹, muscle fatigue², glucose-related pathologies, and others. When compared to the electrical stimulation of peripheral nerves, there are numerous advantages: the ability to target molecularly defined subtypes, access to opsins engendering neural inhibition, and optical recruitment of motor axons in a fashion that mimics natural recruitment², which eliminates the fatigue roadblock inherent to functional electrical stimulation (FES)⁴.

15 **[0003]** The retrograde transfection of AAV6-hSyn-ChR2-YFP, injected intramuscularly, has been shown to result in a repeatable muscle activation in response to *direct* optical stimulation of the peroneal and tibial nerves⁵. Direct illumination was accomplished using several different invasive techniques: the exposed nerve illuminated with a free-space optical source⁵, an LED-based optical nerve cuff², and a fiber-optic-based optical nerve cuff⁵. These invasive methods were relied upon to provide a sufficiently high fluence rate to activate the target opsins expressed in the nerves. A *transdermal* illumination approach was successfully pursued for suppressing pain receptors in mice via stimulation of superficial cutaneous nociceptors¹. Transdermal illumination has been postulated to target pain and touch fibers due to their superficial nature; deep-tissue targets were previously considered optically inaccessible because of the significant attenuation of blue light in biological tissue^{6,7}. Transdermal stimulation of sensory axons in the sciatic nerve of transgenic mice has been previously linked to cortical recordings, yet it is unclear the extent to which cutaneous co-activation affected the measurements⁸.

25 **[0004]** There have been several optogenetics studies leveraging non-invasive illumination in the brain. Both trans-cortical optical stimulation of ChR2-expressing neurons⁹ and trans-cortical neural silencing using the red-shifted opsin Jaws¹⁰ could reliably activate and inhibit neural populations respectively, the latter due to the improved penetration of red light in tissue; both experiments, however, required a fiber implant beneath the skin. Recent work in the vibrissa motor cortex of an awake, head-fixed mouse demonstrated optogenetic stimulation through bone and skin using both the red-light opsin ReaChR and ChR2, although the degree of movement was superior with ReaChR, which could produce reliable vibrissa motions up to 10 mm from the skin surface¹¹. Direct transdermal optogenetic control of smooth muscle in rats¹² and skeletal muscle in transgenic mice¹³ has been demonstrated. However, nerve targets are smaller and deeper than muscle targets, and represent a greater challenge to the transdermal approach. Infrared neural stimulation has also been presented as a promising optogenetics alternative that may theoretically produce anatomically selective, transdermal stimulation without modification of target tissue. However, major concerns include heating-induced tissue damage, non-selective co-stimulation of sensory and motor fibers, and difficulty localizing the target nerves¹⁴.

35 **[0005]** However, peripheral nerves are located beneath several tissue types, including skin, blood vessels, adipose tissue, and muscle. These tissues strongly attenuate visible light, preventing the majority of delivered light from reaching the target nerve.

40 **[0006]** Existing prior art includes WO 2007/024391, which relates to light-activated ion channel proteins that can generate millisecond-timescale electrical spikes when incorporated into neurons and illuminated with rapid pulses of light; and WO 2012/061684, which relates to compositions comprising lanthanide-doped nanoparticles which upconvert electromagnetic radiation from infrared or near infrared wavelengths into the visible light spectrum. Further, US 2011/144723 discloses a wearable device using light stimulation to reduce palsies or tremors as well as to mitigate neural damage caused by injuries, diseases and intoxications.

SUMMARY OF THE DISCLOSURE

50 **[0007]** According to the present invention, there is provided a wearable device as defined by the appended claims. Also described in the specification is a method of stimulating a nerve of mammal, and a wearable device for optogenetic motor control and restoring sensation in a mammal.

55 **[0008]** The specification also discloses a non-claimed method of stimulating a nerve of a mammal, including the steps of optogenetically transforming a nerve in a mammal, wherein the nerve is susceptible to stimulation by selective application of transdermal light, and applying a light source to dermis of the mammal proximate to the optogenetically transduced nerve, thereby stimulating the nerve.

[0009] The specification also discloses a non-claimed method for optogenetically transfecting a mammal, including the step of administering to selected tissue of the mammal genetic material encoding light-sensitive opsins and a neural

promoter, wherein the genetic material causes a transdermal optogenetic peripheral nervous system response to light.

[0010] The specification also discloses a wearable device for optogenetic motor control and restoring sensation of a mammal, including a wearable support, a power source at the wearable support, a controller at the wearable support and in electrical communication with the power source, and a transdermal light source coupled to the controller, the controller driving a light source to direct light from the wearable support and toward the mammal while wearing the support.

[0011] The inventors have discovered that, by injecting a higher overall number of viral particles, more viral copies integrate in the motor neuron genome, thereby translating to a higher density of ChR2 channels in the axon and a sufficiently high optical sensitivity, whereby transdermal, optogenetic control of nerves is possible. Opsin expression levels and muscle response are demonstrated to be a function of injected viral particles (vp) and fluence rate in a rat model.

[0012] This disclosure has several advantages. For example, the method described herein can be employed in the treatment of spinal cord injury, post-polio syndrome, ALS, or other type of CNS-mediated loss of motor function; for neural inhibition, such as can be employed to control chronic pain from the spinal cord nerves, cranial nerves (such as trigeminal neuralgia), or other etiologies. Intra-nerve injections of high-concentration AAV into nerve stumps could produce optogenetically active nerves that can be employed in the method to improve the functionality of current prosthetic devices by providing the much needed "sense of touch" feedback to amputees from their electromechanical devices. The method can also be employed to treat foot-drop, which is a condition in stroke victims characterized by the inability of the patient to dorsiflex during swing phase, resulting in the toes dragging along the ground. Mood disorders, such as depression and epilepsy, can be treated, by selective stimulation of molecularly unique genetically-defined axonal subsets of the vagus nerve, including, for example, stimulation of molecularly-distinct vagus nerve afferents that are differentially expressed in the gut, lungs, heart, allergy, and stomach^{29,30} to thereby selectively reduce or increase gastric pressure, alter motility, inhibit breathing or speed up breathing rates, etc. Additionally, embodiments can be employed to treat erectile dysfunction by injecting retrograde AAV prior to prostate surgery, thereby allowing for full nerve expression in case the nerve is cut during the surgery.

[0013] The methods and devices described herein can control peripheral nerves situated under deep tissue structures with transdermal, optical signals and are of enormous benefit, integrating all of the advantages conferred by optogenetics while averting the drawbacks associated with implantable devices, such as mechanical failure, device tissue heating, and a chronic foreign body response.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] The foregoing will be apparent from the following more particular description of example embodiments, as illustrated in the accompanying drawings in which like reference characters refer to the same parts throughout the different views. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating embodiments.

[0015] The invention is defined in the claims. Methods of treatment by therapy and surgery are not a part of the invention.

FIGs. 1A and 1B are perspective views of a wrist band light source employed in one embodiment of the invention.

FIGs. 2A and 2B are perspective views of a light source adhering to a wrist of a subject.

FIGs. 3A and 3B are perspective and side views, respectively, of a knee strap with a light source as applied to a knee of a subject.

FIGs. 4A and 4B are perspective views of a light source adhering to skin near a knee of a subject.

FIGs. 5A and 5B are perspective views of a neck strap with a light source suitable for use with another embodiment.

FIGs. 6A and 6B are perspective views of a light source adhering to a neck of a subject.

FIG. 7 is a representation of general architecture for closed-loop feedback control employing physiological sensors in one embodiment of the invention.

FIG. 8 is a schematic representation of a closed loop controller architecture suitable for use with the wearable device of the invention, and directed to motor control.

FIG. 9 is a schematic representation of a closed loop controller architecture suitable for use with the wearable device of the invention, and directed to treatment of depression.

FIG. 10 is a schematic representation of a closed loop controller architecture suitable for use with the wearable device of the invention, and directed to treatment of foot drop.

FIG. 11 is a schematic representation of direct fluence rate measurement.

FIG. 12 is a schematic representation of transdermal optogenetic stimulation of a nerve with EMG recording in muscles.

FIG. 13 is a Hematoxylin & Eosin ("H&E") cross-section to measure tissue depth in an 8-week female rat showing the peroneal nerve (p.n.) (arrow) adjacent to proximal tibia at most superficial location of the nerve with i. skin, ii. connective tissue, iii. muscle, iv. connective tissue, v. epineurium (BF=biceps femoris, LG=Lateral Gastrocnemius (GN), EDL= Extensor Digitorum Longus); scale bar 1mm.

FIG. 14 are representations of common peroneal nerve (c.p.n.) and tibial nerve (t.n.) depths by tissue type by rat

age compared to human median nerve (m.n.) and ulnar nerve (u.n.) depths at adult wrist.

FIG. 15 is a plot of Monte Carlo ("MC") estimated normalized fluence rate as a function of distance from skin normalized to incident power for a 200 g rat.

FIG. 16 is an example of a biphasic EMG twitch waveform generated by the tibialis anterior (TA) muscle in response to transdermal illumination of the proximal tibia (160 mW laser power).

FIG. 17 is a representation of variation in transdermal (3, 5, 8 weeks) and direct-nerve (8 weeks) optical response as a function of dosage and age.

FIG. 18 is a representation of calculated RMS EMG voltage in TA at 5 weeks post-injection for 5 s transdermal stimulation: n=2 (1 Hz, 15 ms pulse width (PW), 160 mW skin surface power).

FIG. 19 is a representation of calculated RMS EMG voltage in TA as a function of incident power and frequency for 5 s transdermal stimulation for P2 neonate at 5 weeks post-injection: n=1 (10 ms PW).

FIG. 20 is a representation of RMS voltage showing selective stimulation of TA without GN in response to illumination at proximal tibia: n=2 (1 Hz, 10 ms PW, 160 mW skin surface power).

FIG. 21 is a plot of ankle angle as a function of light position as a laser was moved between proximal tibia and mid-calf corresponding to c.p.n and t.n., respectively, and wherein the horizontal axis normalized over ~8 mm distance between illumination regions; position data smoothed with 30 point moving average filter: n=1.

FIG. 22 is a representation of ankle angle as laser power at a proximal tibia is ramped up from 5 mW to 160 mW (violet) and back down to 5 mW (blue): n=2.

FIG. 23 are photographs and representations of P2 neonate sciatic nerve (s.n.) labeled for CHAT (green) and ChR2 (red) with corresponding counts in both the c.p.n. (targeted) and t.n. (non-targeted): scale bar 12.5 μm (top) and 150 μm (bottom).

FIG. 24 is an annotated photograph of a half-section of right spinal cord of P2 neonate between L3-S 1 labeled for ChR2 (red) and DAPI (blue). Within white matter, laminae I-IV & IX are outlined and likely nucleus proprius (arrow) and dorsal nucleus of Clarke (arrowhead). Within grey matter, gracile fasciculus (G.F.) outlined: scale bar 325 μm .

FIG. 25 are photographs and histograms illustrating serial dilution of anti-GFP primary antibody to evaluate relative opsin density between low-dose and high-dose P2 injections, with 1: 100 and 1:2000 dilutions shown: scale bar 17.5 μm ; comparison of transduction efficiency vs. primary antibody concentration shown in both total axon count and summed fluorescence of all ChR2+ axons for both doses.

DETAILED DESCRIPTION OF THE INVENTION

[0016] The invention includes transdermal optogenetic peripheral nerve stimulation.

[0017] A non-claimed method of stimulating a nerve of a mammal, includes the steps of optogenetically transforming a nerve in a mammal, wherein the nerve is susceptible to stimulation by selective application of transdermal light, and applying a light source to dermis of the mammal proximate to the optogenetically transduced nerve, thereby stimulating the nerve. In one example the method further includes the step of actuating at least one sensor as a consequence of sensing at least one effect of the light source on the mammal by stimulation of the optogenetically transduced nerve, whereby the sensor generates a signal. In still another example, the method further includes the step of processing the signal through a computational control element that, in response to the signal, provides a feedback control signal that modulates the light source and subsequent stimulation of the optogenetically transduced nerve.

[0018] Another exemplary, non-claimed method is a method of optogenetically transfecting a mammal, including the step of administering to selected tissue of the mammal genetic material encoding light-sensitive opsins and a neural promoter, wherein genetic material causes a transdermal optogenetic peripheral nervous system response to light. In one such example, the genetic material includes viral particles that operate as a viral vector to carry the genetic material. In a specific example, the viral particles are adeno-associated viral (AAV) particles. In one example, the adeno-associated viral particles can include at least one member selected from the group consisting of serotype 1, serotype 2, serotype 3, serotype 4, serotype 5, serotype 6, serotype 7, serotype 8, serotype 9, serotype 10 and serotype 11. In one particular example, the viral vector is AAV6-hSyn-ChR2 (H134R)-EYFP. The genetic material can be administered at a value of at least 10^{14} copies of DNA per milliliter at an approximate injected volume scaled to the weight of the mammal. For example, the injected volume can be at least 10 μL per kilogram total animal weight of the mammal. In another embodiment, the genetic material is administered at a volume of at least 10^{11} copies of DNA per kilogram in a mammal. The viral vector can be administered, for example, by at least one method selected from the group consisting of intramuscular injection, sub-epineurial injection, and electroporation. In one example, the tissue of the mammal to be transfected is within about 4 cm of a dermal surface of the mammal. In another embodiment, the light-sensitive opsin includes at least one member of the group consisting of ChR2(H134R), ReaChR, Chrimson, Chrimson Rs, Chrimson Cs, Chrimson R, CoChR and JAWS. In another specific example, the neural promoter includes at least one member of the group consisting of hSyn, CamKII, hThy-1UflaCAG, SST and hypocretin. In one example, the tissue is at least one member of the group consisting of a nociceptive fiber, a motor neuron, a spindle fiber, a golgi tendon organ, a cutaneous fiber, a low threshold

mechano-receptor (LTNR), a nerve stent, a common peroneal nerve, a vagus nerve, a cavernous nerve, a median nerve, an ulnar nerve, a radian nerve, a tibial nerve, a median plantar nerve, a sciatic nerve, a superficial peroneal nerve, a cavernosa nerve, a deep peroneal nerve, a sural nerve, a recurrent laryngeal nerve, and a musculocutaneous nerve.

[0019] The invention is a wearable device for optogenetic motor control and restoring sensation in a mammal, including a wearable support, a power source at the wearable support, a controller at the wearable support and in electrical communication with the power source, and a transdermal light source coupled to the controller, the controller driving the light source to direct light from the wearable support and toward the mammal while wearing the support. In one specific embodiment, the wearable support is a strap. In a specific embodiment, the strap is a member selected consisting of a wrist strap, a knee strap, a necklace, a headband, an ankle strap, a leg strap, a stomach strap, and an arm strap. In another embodiment, the wearable support is an adhesive patch. In still another embodiment, the transdermal light source includes at least one member selected from the group consisting of a light emitting diode (LED), diode-pumped solid-state (DPSS) laser, a diode laser, a solid-state laser, a vertical-cavity surface emitting laser (VCSEL), and an edge emitting laser diode (EELD). In one embodiment, the light source is of a type that emits a wavelength in a range of between about 300 nm and about 1100 nm. The wearable device includes at least one sensor in communication with the controller, whereby the at least one sensor provides sensory feedback to the controller which controls the light source to thereby selectively stimulate at least one optogenetically altered nerve. In one such embodiment, the sensory feedback is at least one member of the group consisting of cutaneous feedback and proprioceptive feedback. In a specific embodiment, the sensor is selected from the group consisting of an accelerometer, a position sensor, a torque sensor, and a gyroscope. In still another embodiment of the invention, the controller of the wearable device includes at least one member of the group consisting of a reflexive controller, a state-based controller and a pattern-recognition controller.

[0020] Using intramuscular or sub-epineurial injections of a viral vector or other DNA-mediated platform (such as electroporation) for transduction of genetic material into biological tissue, neurons in peripheral nerves can be transduced to functionally express an opsin along the entire length of the axon and its membrane. An opsin has the unique ability to enable the flow of ions in response to illumination with a specific wavelength of light. Sufficient ion flow leads to an action potential, which is an electrical signal that nerves use to control target tissue. The likelihood of an action potential depends on several variables including: 1) the density of opsin channels within the axon (driven by the concentration of injected particles, the total volume injected, the efficiency of transduction, and the diffusion of that genetic material), 2) properties inherent to the opsin itself including photocurrents and kinetics, and 3) optical variables including the power, shape, pulse train, and wavelength of light used to depolarize the axon. If the first two variables are optimized to provide high photocurrents and high opsin expression, it is theoretically possible to decrease the power of light required as described by the previously mentioned 3rd variable. The optical sensitivity of nerves can be increased to such an extent as to allow for stimulation of nerves beneath the tissue surface with *transdermal* illumination. This adds a fourth anatomical variable to be considered, which comprises the distance between the nerve and the skin surface, the axon's relative position within the cross-section of the nerve, and the optical absorption and scattering properties of the tissues between the nerve and the skin.

[0021] There is disclosed a non-claimed method encompassing injection of a specific adeno-associated virus (AAV) serotype 6 into a nerve or muscle in an amount sufficient to optogenetically transfect the target tissue. In a specific embodiment, the AAV6 virus containing the light-sensitive opsin ChR2(H134R), a neuron-specific promoter (hSyn), and a tissue-marker (EYFP), and a high-concentration of viral particles (e.g. 1.0E14 vp/mL) was employed, as well as a method of repeated high-volume follow-up intramuscular and intra-nerve injections. As a result, opsin expression in the tissues was so strong as to enable nerve stimulation at low levels of incident light. Specifically, for nerves at a tissue depth of ~2mm, muscle twitches were observed at an estimated nerve surface power of ~100 μ W/mm². Despite the strong scattering properties of blue light in biological tissues, ~100 μ W/mm² at 2mm depth can be produced with incident light power at the surface of the skin of ~10mW/mm², a rate which can be provided by a traditional low power laser pointer. Likewise, responses at up to 4mm depth were produced with a higher incident power at the surface of the skin, up to ~160mW/mm², such as can be provided by an LED array, demonstrating that wearable devices can control key aspects of human physiological function controlled by peripheral nerves without requiring any implants or even direct contact with skin.

[0022] There are several nerves, which are close enough to the skin to be appropriately targeted for transdermal peripheral nerve optogenetics. These include the nerves of the hand, leg, neck, and perineum. Some major nerve trunks, which run ~2cm or less from the surface of the skin are listed in Table 1 below. Also shown are disease applications for the target nerve.

TABLE 1

Nerve	Location	Innervates	Distance From Skin	Disease Application	Technology
Median N.	Wrist	Hand sensation and intrinsic muscles	3.2mm	Paralysis, amputation, pain	LED Wristband
Ulnar N.	Wrist	Hand sensation and intrinsic muscles	2.1mm	Paralysis, amputation, pain	LED Wristband
Radial N.	Elbow	Upper Limb Extensors	~1cm	Paralysis, amputation, pain	LED Elbow Brace
Common Peroneal N.	Knee	Foot Dorsiflexors	8mm-1cm	Paralysis, foot-drop for stroke victims, pain	LED knee brace
Cavernosal N.	Perineum	Corpus Spongiosum	~1cm	Erectile Dysfunction	LED underwear
Vagus N.	Neck	Gut, Stomach, Heart, Lungs, Brain	~1.7cm	Obesity, Anorexia, IBD, Diabetes, Depression, Epilepsy	LED necklace
Tibial N.	Knee	Foot Plantarflexors and sensation	~2cm	Paralysis, amputation, pain	LED knee brace

[0023] The method can be employed in many types of devices. For example, in one embodiment, the invention is a wearable device 100, 200 that is an illuminated wristband 105 or patch 205 for optogenetic motor control and sensation restoration in the hand, and includes a rechargeable battery and microcontroller, light source (e.g., LED) casing, a transdermal light, and an adhesive layer, as shown in FIGs. 1A, 1B, 2A and 2B, where "a" is a power source (e.g. battery), "b" is a light emitter (e.g. LED), "c" is a light (e.g., 470 nm), and "d" is an adhesive material (e.g., methacrylate). The wearable device 100, 200 includes a wearable support 105, 205, a power source "a" at the wearable support, a controller at the wearable support (e.g., integrated into the support) and in electrical communication with the power source, and a transdermal light source "b" coupled to the controller. The controller drives the light source to direct light "c" from the wearable support and toward the mammal while wearing the support.

[0024] LEDs positioned in proximity to the median and ulnar nerves and a rechargeable battery may be encased in an ergonomic wristband. Although typically blue, the wavelength can be tailored to the wavelength required for the specific opsin injected. Depending on anatomy and power requirements, the device may or may not have a cooling system comprising a heatsink or fluid system to prevent burns at the surface. Microcontrollers inside the device control the frequency, power, and duty cycle of the delivered light. Optogenetic stimulation of the median and ulnar nerves at the wrist (depicted here) provide fine motor control to intrinsic hand muscles including the lumbricals, the flexor pollicis brevis, the abductor pollicis, and others. In addition, targeted stimulation of sensory fibers could provide cutaneous or proprioceptive sensory feedback from touch sensors located on prosthetic fingers or hands. The form of the device can be either a wristband, as shown in FIGs. 1A and 1B, or an adhesive patch as shown in FIGs. 2A and 2B. A patch is affixed to the skin by a suitable biocompatible adhesive, such as is known in the art.

[0025] In another embodiment, the invention is an illuminated knee brace device 300 including wearable support 305, as shown in FIGs. 3A and 3B, or a patch device 400 including wearable support 405, as shown in FIGs. 4A and 4B, for optogenetic treatment of paralysis and foot-drop syndrome. The letters "a," "b," "c," and "d," reference the same components indicated in FIGs. 1A, 1B, 2A and 2B. For example, LEDs positioned outside the common peroneal nerve as well as a rechargeable battery may be fitted to a knee brace. This allows the device to be secure while not restricting user motion. Although typically blue, the wavelength can be tailored to the specific opsin injected. Depending on anatomy and power requirements, the device 300, 400 may or may not have a cooling system comprising a heatsink or fluid system to prevent burns at the surface. Microcontrollers inside the device 300, 400 (e.g., integrated into support 305, 405) control the frequency, power, and duty cycle of the delivered light. Optogenetic stimulation of the common peroneal nerve (depicted here) provides motor control over dorsiflexors in the foot. In foot-drop or paralysis, this technology causes muscles, including the tibialis anterior, extensor digitorum longus, and others, to fire based on sensors in the device that track the leg state including, but not limited to, accelerometers, position sensors, torque sensors, gyroscopes, etc. Optionally, suitable controllers, such as reflexive controllers, state-based controllers, or pattern-recognition controllers, can be employed. Also, other nerves can be employed by the wearable device of the invention such as the tibial nerve (not depicted), as well as its innervating muscles, although the tibial nerve lies about twice as deep as the peroneal

nerve. In various embodiments, controllers can be used assist gait by firing at the proper time in paralysis. The design can take the form of a knee brace or a patch, for example. The knee brace itself, in various embodiments, can include an elastomer, fabric, silicone, or a suitable plastic material, such as with an exterior designed to remain aesthetically pleasing to the user. The patch embodiment of the wearable device of the invention can employ a suitable biocompatible adhesive, such as an acrylic or hydrocolloid. In one embodiment, there is a patch for each nerve, or a single patch with LEDs targeted to each nerve.

[0026] Still another embodiment of the wearable device of the invention is an illuminated necklace or patch for optogenetic treatment of vagus-implicated disorders. In one embodiment, LEDs and a rechargeable battery are encased within a necklace device 500 including wearable support 505, as illustrated in FIGs. 5A and 5B. The exterior may be designed to remain aesthetically pleasing to the user. This allows the device to be secure while not restricting user motion. Although typically blue, the wavelength can be tailored to the wavelength required for the specific opsin injected. Depending on anatomy and power requirements, the device may or may not have a cooling system comprising a heatsink or fluid system to prevent burns at a skin surface. Suitable microcontrollers, such as are known in the art, inside the device 500 variously control the frequency, power, and duty cycle of the delivered light. Optogenetic stimulation of the vagus nerve (represented in FIGs. 5A and 5B), for example, optionally provide autonomic control and sensation from its fibers in the gastrointestinal tract, heart, lungs, as well as treatment of mood and seizures through downstream neurological and endocrine pathways. The letters "a," "b," "c," and "d" correspond to the same items referenced in the previous drawings. This embodiment of the wearable device of the invention is employed, for example, to treat diseases defined by optogenetically targeting molecular-specific subtypes in the vagus nerve. The necklace or patch design can be customized to the individual. Suitable materials of construction of the necklace or patch include, for example, an elastomer, fabric, silicone, or plastic material. Another embodiment of a wearable device of the invention, shown in FIGs. 6A and 6B, is configured as a patch device 600 including wearable support 605 that is affixed to skin by a suitable biocompatible adhesive, such as an acrylic or hydrocolloid.

[0027] In still another embodiment, the invention includes a generalized control architecture for closed-loop transdermal optogenetic stimulation. In this embodiment, output physiology (e.g., position, velocity, pain, appetite, etc.) of a wearable device of the invention is modulated in a closed-loop fashion by a transdermal method. FIG. 7 is a schematic representation of a control diagram suitable for employment in wearable devices (e.g., devices 100, 200, 300, 400, 500, 600) of the invention. As shown in FIG. 7, input sensors measure desired physiology, such as sweat, and movement sensors or neural signals, or a button press for manual control of a human emotional state as the closed-loop physiology change, along with wireless transmission capabilities. A microcontroller processes input signals from input sensors within a specific control strategy (such as defined above, and others that include, for example, reflexive, state-based or pattern recognition control) and output a desired signal (such as power, frequency, duty cycle, #LEDs) following data analysis of the input signals. A current source demultiplexes the input signal into individual currents for each light source channel. A light source, such as a high-powered LED or a DPSS laser, optimally emits light at a specific frequency through the skin to effect a change in output physiology, as described above, such as physical movement, pain relief, appetite change, mood improvement, sexual arousal, or others. The output of physiology sensors, and the model and line-output from the microcontroller, are for further processing or to be saved for model. The specific control architecture will be tailored for the specific application employed.

[0028] While FIG. 7 is a representation the general architecture for closed-loop feedback within one patient in one embodiment of the invention, patients may be coupled to one another, so that the input signal for one patient is driven by an output change in physiology from another patient. These can be linked by several technologies including Bluetooth (BT), Bluetooth Low Energy (BLE), Near Field (NFC), and Radiofrequency Communication (RF). Optionally, smartphones, as the processor and wireless communication device, can be employed both for a single individual, and coupling two or more individuals together. In this way, appetite control, for example, can be socially reinforced, so that when one person at a table is satiated, other individuals also begin to feel full. Alternatively, emotional states can be coupled so that when one individual feels compassionate as measured by certain sensors that can stimulate empathy in another individual.

[0029] FIG. 8 is a schematic representation of a closed loop controller architecture suitable for use with the wearable device (e.g., device 100, 200) of the invention, and directed to motor control. In this figure, a change in muscle state as measured by certain physiological sensors including, but not limited to, electromyography electrodes, accelerometers, sono crystals, position sensors, and others, is used as the input to drive illumination of the optogenetically active nerve, which results in a physical movement owing to nerve-drive contraction of the muscle. This can be employed, for example, in restoration of fine motor control tasks in paralyzed individuals.

[0030] FIG. 9 is a schematic representation of a closed loop controller architecture suitable for use with the wearable device (e.g., device 500, 600) of the invention, and directed to treatment of depression. In this diagram, mood is measured through certain physiology sensors that can include, but are not limited to, electroencephalography, electrocorticography, smartphone data based on user-device interactions, or direct user input. A microcontroller processes these data and uses them to provide input of certain temporal, frequency, amplitude, and phase characteristics to a light source located

transdermal to the vagus nerve of an affected individual. Vagus nerve stimulation may result in an alleviation of symptoms and improve depressive behaviour symptoms, which in turn, will be tracked by the physiology sensors.

[0031] FIG. 10 is a schematic representation of a closed loop controller architecture suitable for use with the wearable device (e.g., device 300, 400) of the invention, and directed to treatment of foot drop. In this diagram, position is measured during a gait cycle by employing sensors, such as accelerometers, stretch sensors, encoders, torque sensors or others on the same limb or on the opposite limb. These data are fed into a microcontroller, which employs an algorithm to interpret the appropriate position of the gait cycle. When the limb reaches the desired portion of the gait cycle to initiate stimulation, the microcontroller sends a signal to the current source which drives the light source required for optogenetic activation of the target nerve and downstream muscles. This results in a physical change (e.g., dorsiflexion in foot drop), which can restore an individual's functional gait. This change can be tracked in real-time through the closed-loop system to provide the appropriate physical state output required for optogenetically enhanced gait.

[0032] The following are representative examples of various embodiments of the invention.

EXEMPLIFICATION

Methods

[0033] All animal experiments were conducted on Fischer 344 rats under the supervision of the Committee on Animal Care at the Massachusetts Institute of Technology.

[0034] To measure the thickness and type of tissue between the skin surface and target nerve, a critical factor in determining how much light reaches the different nerve depths, the right hindlimbs of four 5-week old and four 8-week old Fischer 344 rats were extracted, postfixed for 48 hours in 4% paraformaldehyde (PFA), decalcified 36 hours in acetic acid, paraffin processed, embedded, sectioned at 25 μm thickness every $\sim 250 \mu\text{m}$, and stained with H&E. The sciatic nerve (s.n.) was traced to its division into the common peroneal nerve (c.p.n.) and tibial nerve (t.n.), which were followed distally, slice by slice, to their end plates at the tibialis anterior muscle (TA) and gastrocnemius muscle (GN), respectively. The c.p.n. and t.n. depth, relative to skin, was measured on each slice; the slice with the minimum distance between nerve and skin surface was conservatively used for gathering the tissue geometry required for modeling. A Monte Carlo (MC) simulation was created for estimating fluence rate distribution in the rat c.p.n. and t.n. Key inputs to the model included tissue geometry, attenuation coefficients for scattering (μ_s) and absorption (μ_a), and anisotropy factors in skin, muscle, connective tissue, epineurium and nerve, which were gathered from previous studies¹⁵⁻¹⁸.

[0035] To validate the fluence rate simulation and its applicability to other geometries, a direct measurement of fluence rate was pursued. A method previously used to measure fluence rate in a directionally isometric and minimally invasive manner involves a small ruby sphere directly coupled to a fiber-optic cable¹⁹. The measured intensity of the ruby's emission at its spectral peak of $\sim 694 \text{ nm}$ is directly dependent on fluence rate. The device was constructed by attaching a 400 μm diameter ruby sphere (Edmund Optics) to the polished edge of a multimode fiber optic cable with 400 μm core and 25 μm cladding (ThorLabs) with UV-curing epoxy (ThorLabs). The other end of the fiber optic cable was connected to a spectrometer (ThorLabs). The system was calibrated by illuminating the ruby sphere at known fluence rates with a DPSS 473 nm laser (OptoEngine) and measuring the spectrometer intensity at 694 nm. To measure direct fluence rate in vivo, a 5 mm skin incision was made at the lateral femur in two female, 200 g Fischer 344 rats. The isometric probe was inserted at the incision and routed distally into three separate regions of interest: 1) the subcutaneous space at the mid-tibia, 2) the c.p.n. at its most superficial location, and 3) the t.n. at its most superficial location. Spectrometer intensity at 694 nm was measured with transdermal, 473 nm illumination for a range of powers, and translated to fluence rate using the calibration described above, and represented schematically in FIG. 11.

[0036] Viral vectors were produced in two batches enabling four dosages in five 8 week adult Fischer 344 rats (low, medium, high, and highest), and two dosages in ten neonate Fischer 344 rats (low and high). Low- and medium-dose AAV6-hSyn-ChR2(H134R)-EYFP viral vectors were produced from the Vector Core facility at the University of North Carolina Chapel Hill, provided in a concentrated dosage ($1.4 \times 10^{13} \text{ vp/mL}$). The hSyn promoter was employed to restrict optogenetic activation to nerve tissue, which was validated by directly illuminating the injected muscles and noting the lack of response. At the time of surgery, the thawed vector was diluted with 0.9% sterile saline to $2.8 \times 10^{12} \text{ vp/mL}$ and $9.1 \times 10^{12} \text{ vp/mL}$ for the low-dose and med-dose adult Fischer 344 rats respectively; the low-dose neonates were injected 2 days postpartum (P2) with $1.4 \times 10^{13} \text{ vg/mL}$ virus as received. Ultra-high concentration AAV6-hSyn-ChR2(H134R)-EYFP viral vector was procured from Virovek Inc., at a titer of $1.2 \times 10^{14} \text{ vp/mL}$, and injected undiluted into the high- and highest-dose adult and high-dose P2 neonates. This high concentration ($\sim 10^{14} \text{ vp/mL}$) enabled the high multiplicity of infection which resulted in the transdermal response. The injected volume was scaled to total animal weight at a volume of approximately 150 μL per kg weight during injection. Each animal showing transdermal expression therefore received at least 10^{11} viral copies of opsin DNA with the highest animals at 5×10^{12} total viral particles (for a 150g adult rat) or 1×10^{12} total viral particles (for a 25g neonate rat) which both equal roughly $3\text{-}5 \times 10^{13}$ viral copies per kg.

[0037] Fifteen rats (Charles River Laboratories) were housed under a 12:12 light dark cycle in a temperature-controlled

environment with food and water ad libitum. Under isoflurane anesthesia, a 1 cm skin incision was made over the tibia in the adults and the biceps femoris (BF) muscle was reflected from its proximal insertion at the tibia to reveal the c.p.n.'s synaptic junction at the TA end plate. 75 μL of virus was intramuscularly injected in 3 regions of TA muscle within 1 cm of the end plate at a speed of 5 $\mu\text{L}/\text{min}$ with an additional 5 μL of virus directly injected into the c.p.n. at the end plate at a speed of 1 $\mu\text{L}/\text{min}$, totaling 1.8×10^{11} vp and 7.3×10^{11} vp for the low- and medium-dose adults respectively. For the high- and highest-dose adults, a total of 20 μL and 35 μL was injected at 5 $\mu\text{L}/\text{min}$ into the TA with an additional 5 μL of virus injected at 1 $\mu\text{L}/\text{min}$ directly into the c.p.n. at the end plate, totaling 3.0×10^{12} vp and 4.8×10^{12} vp respectively. In the five low-dose P2 neonate rats, 2 μL was injected through the skin into the TA at 1 $\mu\text{L}/\text{min}$ totaling 2.8×10^{10} vp. For the high-dose P2 neonate rats, 5 μL was injected through the skin into the TA at 1 $\mu\text{L}/\text{min}$; two weeks following, the right hindlimbs of the same animals were opened in the same method as the adults and 4 μL was injected directly into the TA at the c.p.n. endplate with an additional 1 μL into the nerve at 1 $\mu\text{L}/\text{min}$ totaling 12×10^{12} vp. Following all open injections, the BF was sutured with 5-0 vicryl, and the skin was closed with wound clips and tissue glue.

[0038] For each animal, a twitch response to 473 nm transdermal light was tested at 3, 5 and 8 weeks post-injection. At 8 weeks, direct optical stimulation of the nerve was also tested. To measure the strength of nerve responses, four 30G monopolar electromyography (EMG) needles (Natus Medical) were directly inserted through the skin into the GN and TA for bipolar recording; a ground electrode was placed subcutaneously at the back. Careful needle placement limited acute inflammation at the illumination site. Needles were connected to a 20 kS/s multi-channel amplifier with a fixed 200x gain (IntanTech). A 473 nm laser (OptoEngine) was secured above the anesthetized animal to a stage assembly allowing for six degrees of freedom, as represented schematically in FIG. 12. The laser beam had a Gaussian cross-sectional profile and 3 mm diameter ($1/e^2$). Electrical signals controlling the laser parameters were simultaneously recorded by the amplifier, enabling temporal synchronization of laser pulses and EMG. Data analysis was performed in MATLAB software (The Mathworks, Inc.).

[0039] Following direct nerve illumination, rats were anesthetized and transcardially perfused with 4% PFA in PBS. Spinal cord, TA, and s.n. were dissected, post-fixed for 12 hours, paraffin processed, embedded, and sectioned at 10 μm . EYFP expression was amplified with Rb pAb anti-GFP (ab290, Abcam) at 1:200 (unless specified) with Alexa Fluor 568 (Fisher); s.n. was labeled with gt anti-CHAT (AB144P, Millipore) at 1:100 and Alexa Fluor 488 (Fisher), all in 1% w/v BSA in PBS-T. Immunofluorescence images were taken on an Evos FL Auto (Fisher) epifluorescence microscope at 10x and 20x and processed with Imaged.

Results

[0040] The measured tissues between the skin surface and nerve comprised skin, connective tissue, muscle, and epineurium (FIG. 13), with total depth ranging from 1.4 mm for the c.p.n. in the 5-week rat to 5.3 mm for the t.n. in the 8-week rat (FIG. 14). For human comparison, the distance from skin surface to the median and ulnar nerves at the wrist measure 2.1 mm and 3.2 mm respectively²⁰ (FIG. 14). For a 200 g rat, the fluence rate along the centerline below the incident laser as a function of distance shows ~2 orders of magnitude and ~3.5 orders of magnitude declines for the c.p.n. and the t.n. respectively, as shown in FIG. 15.

[0041] Direct fluence rate measurements are shown alongside the MC simulation results in Table 2, showing good agreement with a maximum deviation of 12%. Table 2 shows the normalized fluence rate for 5-week and 8-week rats at the c.p.n. and t.n., as well as for the median nerve and ulnar nerve of a human wrist.

TABLE 2

Fluence Rate (1/mm ²): Normalized to Incident Power			
	Subcutaneous	Peroneal N.	Tibial N.
Direct Measure	$19 \times 10^{-2} \pm 0.2 \times 10^{-2}$	$3.9 \times 10^{-3} \pm 1.0 \times 10^{-2}$	$6.3 \times 10^{-5} \pm 1.2 \times 10^{-5}$
MC Simulation	2.1×10^{-2}	4.0×10^{-3}	5.9×10^{-5}

[0042] As shown therein, the normalized fluence rate was found to be $3.9 \times 10^{-3} \text{ mm}^{-2}$ at the peroneal nerve for the 8-week rat and $1.1 \times 10^{-3} \text{ mm}^{-2}$ at the tibial nerve of a 5-week old rat, as can be seen in Table 3.

TABLE 3

Fluence Rate (1/mm ²): Normalized to Incident Power		
	Peroneal N.	Tibial N
5 week (~80g)	8.9×10^{-3}	1.1×10^{-3}

(continued)

Fluence Rate (1/mm ²): Normalized to Incident Power		
	Peroneal N.	Tibial N
8 week (~135g)	4.2×10^{-3}	6.3×10^{-4}
	Median N.	Ulnar N.
Human wrist	1.9×10^{-2}	6.2×10^{-3}

[0043] As such, a 160 mW, 473 nm laser source, transdermally incident, would yield fluence rates of 624 $\mu\text{W}/\text{mm}^2$ and 176 $\mu\text{W}/\text{mm}^2$ at each of the respective nerves. These values are below the previously published optical threshold for ChR2(H134R) activation in peripheral axons², although cultured neurons have seen activations in this range²¹. The estimates for normalized fluence rate at the surface of the median nerve and ulnar nerve in the human wrist show comparable magnitudes to the rat, with 160mW incident light providing 3 mW/mm² and 992 $\mu\text{W}/\text{mm}^2$ respectively.

[0044] The presence of transdermal optical stimulation was defined by repeatable, temporally synchronized EMG twitches of characteristic triphasic or biphasic pattern, as shown in FIG. 16. Transdermal illumination produced twitches in 7 of the 15 tested animals at 5 weeks post-injection, with an 8th responding at 8 weeks post-injection, as shown in FIG. 17. There appeared to be a relationship between dose and the likelihood of transdermal stimulation in both adults and neonates, as indicated in FIG. 18. However, the stability of the transdermal response was uncertain. At 8 weeks post-injection, 3/5 of the P2 neonates and 1/2 of the highest dose adults previously showing a transdermal response lost the response. These nerves remained optogenetically excitable with direct nerve illumination.

[0045] The transdermal RMS voltage was found to increase as a function of laser power; twitch responses were seen with as low as 10 mW incident power, which corresponds to a Monte Carlo (MC) simulated fluence rate at the surface of the nerve of 89 $\mu\text{W}/\text{mm}^2$, as shown in FIG. 19. In addition, it was found that the transdermal response could target muscles highly specific to laser position on the skin surface, as shown in FIG. 20. Illumination of the skin at the proximal tibia, superficial to the insertion of the p.n. in the TA, resulted in dorsiflexion and stimulation at mid-calf, superficial to the insertion of the t.n. in the GN, resulted in plantarflexion, as can be seen in FIG. 21. Alternating laser position could accurately produce a desired ankle position with little hysteresis or fatigue. In addition, incident power could be modulated to affect ankle position-with the laser targeting the skin superficial to the c.p.n. ramped from 10 mW to 160 mW, the ankle slowly dorsiflexed. A subsequent decrease in power resulted in the return to plantarflexion, although baseline not achieved, likely due to resting tension, as shown in FIG. 22.

[0046] Evaluation of s.n. cross-sections showed strong ChR2+ fluorescence in both c.p.n and t.n. divisions, as represented in FIG. 23. Non-targeted t.n. shows strongest ChR2+ expression in the fascicles directly adjacent to the c.p.n, possibly indicating perineurial crossing of AAV at the level of the s.n. during retrograde transport. Despite the goal of exclusive motor fiber transfection, only 40% and 35% of c.p.n. and t.n. ChR2+ axons co-express CHAT, a marker of motor neurons²². Fluorescence and diameter were measured for each ChR2+/CHAT- fiber to identify if the sensory fibers exclusively comprised the large diameter muscle spindle fibers, but no strong relationship between fluorescence and diameter was found. Histological cross-sections of the spinal cord show strongest expression within the several bright ChR2-eYFP+ motor neurons in the ventral horn of the high-dosed animal (FIG. 24). Sensory fiber transfection is also seen in spinal cord sections with ChR2+ dorsal horn expression appearing strongest in the nucleus proprius, dorsal nucleus of Clarke, and first order fibers of the ipsilateral gracile fasciculus, all of which indicate proprioceptive and touch sensors from the lower limbs (FIG. 24). Faint ChR2+ expression is seen in lamina I of the dorsal horn, indicating few ChR2+ A δ or C fibers, possibly consistent with a protective "foot-tucking" response seen during transdermal foot stimulation of the awake, freely-moving rat.

[0047] To compare relative opsin density between dosages, both ChR2+ axon counts and summed average fluorescence was measured within the s.n. for several concentrations of primary antibody, as represented in FIG. 25. The serial dilution shows an order of magnitude difference between high-dose and low-dose rats in both axon counts and total fluorescence. This difference increases to ~2 orders of magnitude for the axons and ~3 orders of magnitude for the fluorescence as the concentration of primary in blocking solution decreases from 1:100 to 1:800. The relative drop in fluorescence as antibody concentration decreases suggests a weaker density of opsin channels within ChR2+ axons in the low-dose animal, due to non-specific binding out-competing the few ChR2+ antigen sites present within the axons. This histological evidence suggests a higher average opsin channel density per axon in the high-dose animal, providing a mechanistic rationale for the lower fluence required at the axon surface for transdermal stimulation in the high-dose rats.

Discussion

[0048] Transdermal illumination of peripheral nerve targets could be achieved by utilizing ultra-high virus concentration

to inject more viral particles and therefore more transgene copies in the motor neuron genome, translating to a higher density of ChR2 channels in the axon, and a lower fluence rate required for depolarization. The fluence rates at the surface of the nerve (89 $\mu\text{W}/\text{mm}^2$ and 176 $\mu\text{W}/\text{mm}^2$ for the 5-week c.p.n. at 10 mW and t.n. at 160 mW laser power respectively) are both roughly an order of magnitude lower than previously published data on light delivery required for ChR2(H134R) activation², indicating that increasing the total number of AAV particles delivered can improve the sensitivity of optogenetically active axons to illumination.

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[0049]

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[0050] The invention is defined in the claims. Other embodiments, examples, items as well as methods of treatment by therapy or surgery, are not a part of the invention

Claims

1. A wearable device (100; 200; 300; 400; 500; 600) for optogenetic motor control and restoring sensation in a mammal, comprising:
 - a) a wearable support (105; 205; 305; 405; 505; 605) configured to be positioned at a skin surface and in proximity to at least one peripheral nerve of the mammal;
 - b) a power source ('a') at the wearable support;
 - c) a controller at the wearable support and in electrical communication with the power source; and
 - d) a transdermal light source ('b') at the wearable support and coupled to the controller, the controller configured to employ closed loop feedback from at least one sensor in communication with the controller to drive the light source to direct light from the wearable support and directed toward the at least one peripheral nerve of the mammal while wearing the support, the light source emitting light at a wavelength required for a specific opsin to respond to illumination, the specific opsin being of a type that is functionally expressed by an optogenetically altered nerve, the controller controlling at least one of frequency, power, and duty cycle of the directed light to induce muscle contraction for motor control or to provide stimulation of sensory fibers for restoring sensation.
2. The wearable device of claim 1, wherein the wearable support is a strap.
3. The wearable device of claim 2, wherein the strap is a member selected from the group consisting of a wrist strap, a knee strap, a necklace, a headband, ankle strap, leg strap, stomach strap, and an arm strap.
4. The wearable device of claim 1, wherein the wearable support is an adhesive patch.
5. The wearable device of any of claims 1 to 4, wherein the transdermal light source includes at least one member selected from the group consisting of a light emitting diode (LED), diode-pumped solid state (DPSS) laser, diode laser, solid-state laser, vertical-cavity surface emitting laser (VCSEL), and edge emitting laser diode (EELD).
6. The wearable device of any of claim 1 to 4, wherein the light source is of a type that emits a wavelength in a range of between about 300 nm and about 1100 nm.
7. The wearable device of claim 1, further including the at least one sensor in communication with the controller, whereby the at least one sensor provides sensory feedback to the controller which controls the light source to thereby selectively stimulate the at least one nerve.
8. The wearable device of claim 7, wherein the sensory feedback is at least one member of the group consisting of cutaneous feedback and proprioceptive feedback.
9. The wearable device of claim 8, wherein the at least one sensor is selected from the group consisting of an accelerometer, a position sensor, a torque sensor, and a gyroscope.

10. The wearable device of claim 1, wherein the controller includes at least one member of the group consisting of a reflexive controller, a state-based controller, and a pattern-recognition controller.

Patentansprüche

1. Tragbare Vorrichtung (100; 200; 300; 400; 500; 600) zur optogenetischen Motorsteuerung und Wiederherstellung der Empfindungsfähigkeit bei einem Säugetier, umfassend:

- a) eine tragbare Halterung (105; 205; 305; 405; 505; 605), die dafür ausgelegt ist, auf einer Hautoberfläche und in der Nähe mindestens eines peripheren Nervs des Säugetiers angeordnet zu werden;
- b) eine Energiequelle ("a") an der tragbaren Halterung;
- c) eine Steuerung an der tragbaren Halterung und in elektrischer Kommunikationsverbindung mit der Energiequelle; und
- d) eine transdermale Lichtquelle ("b") an der tragbaren Halterung und mit der Steuerung gekoppelt, wobei die Steuerung dafür ausgelegt ist, Rückkopplungsschleifen von mindestens einem Sensor in Kommunikationsverbindung mit der Steuerung zu verwenden, um die Lichtquelle so anzusteuern, dass sie Licht von der tragbaren Halterung auf den mindestens einen peripheren Nerv des Säugetiers richtet, während die Halterung getragen wird, wobei die Lichtquelle Licht mit einer Wellenlänge abstrahlt, die erforderlich ist, damit ein spezifisches Opsin auf die Belichtung reagiert, wobei das spezifische Opsin von einer Art ist, die funktionell durch einen optogenetisch veränderten Nerv exprimiert wird, wobei die Steuerung mindestens entweder die Frequenz, die Energie und/oder das Tastverhältnis des gerichteten Lichts steuert, um eine Muskelkontraktion zur Motorsteuerung zu induzieren oder eine Stimulation der sensorischen Fasern zur Wiederherstellung der Empfindung bereitzustellen.

2. Tragbare Vorrichtung nach Anspruch 1, wobei die tragbare Halterung ein Gurt ist.

3. Tragbare Vorrichtung nach Anspruch 2, wobei der Gurt ein Element ist, das aus der Gruppe ausgewählt ist, die aus einem Handgelenkgurt, einem Kniegurt, einer Halskette, einem Stirnband, einem Knöchelgurt, einem Beingurt, einem Bauchgurt und einem Armgurt besteht.

4. Tragbare Vorrichtung nach Anspruch 1, wobei die tragbare Halterung ein Klebpflaster ist.

5. Tragbare Vorrichtung nach einem der Ansprüche 1 bis 4, wobei die transdermale Lichtquelle mindestens ein Element umfasst, das aus der Gruppe ausgewählt ist, die aus einer Leuchtdiode (LED, Light Emitting Diode), einem diodengepumpten Festkörper (DPSS, Diode-Pumped Solid State) -Laser, einem Diodenlaser, einem Festkörperlaser, einem oberflächenemittierenden Laser mit vertikalem Resonator (VCSEL, Vertical-Cavity Surface Emitting Laser) und einer kantenemittierenden Laserdiode (EELD, Edge Emitting Laser Diode) besteht.

6. Tragbare Vorrichtung nach einem der Ansprüche 1 bis 4, wobei die Lichtquelle von einer Art ist, die eine Wellenlänge in einem Bereich zwischen etwa 300 nm und etwa 1100 nm emittiert.

7. Tragbare Vorrichtung nach Anspruch 1, die ferner den mindestens einen Sensor in Kommunikationsverbindung mit der Steuerung umfasst, wobei der mindestens eine Sensor eine sensorische Rückkopplung an die Steuerung bereitstellt, die die Lichtquelle steuert, um dadurch selektiv den mindestens einen Nerv zu stimulieren.

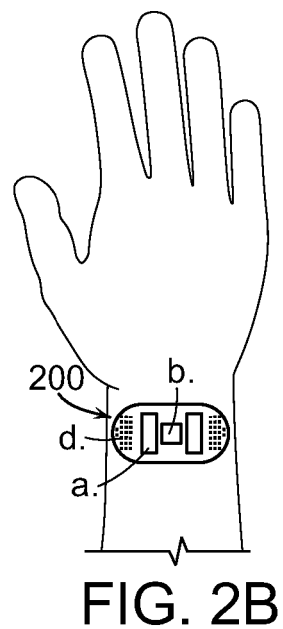
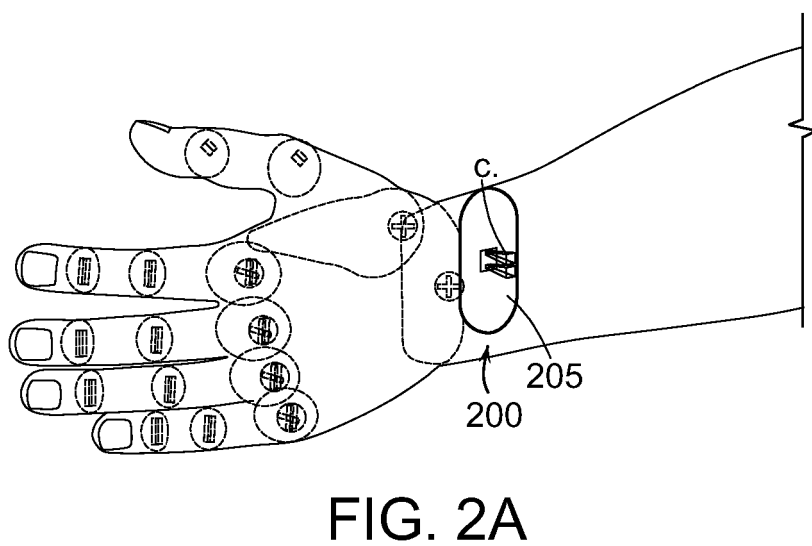
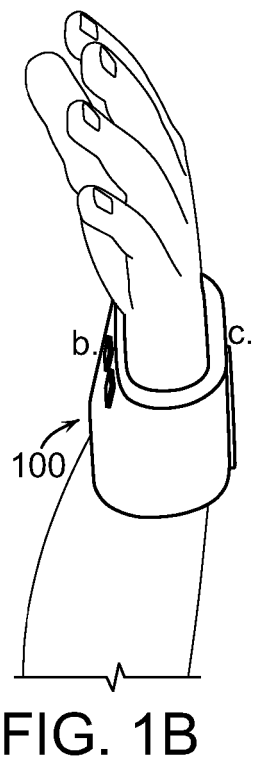
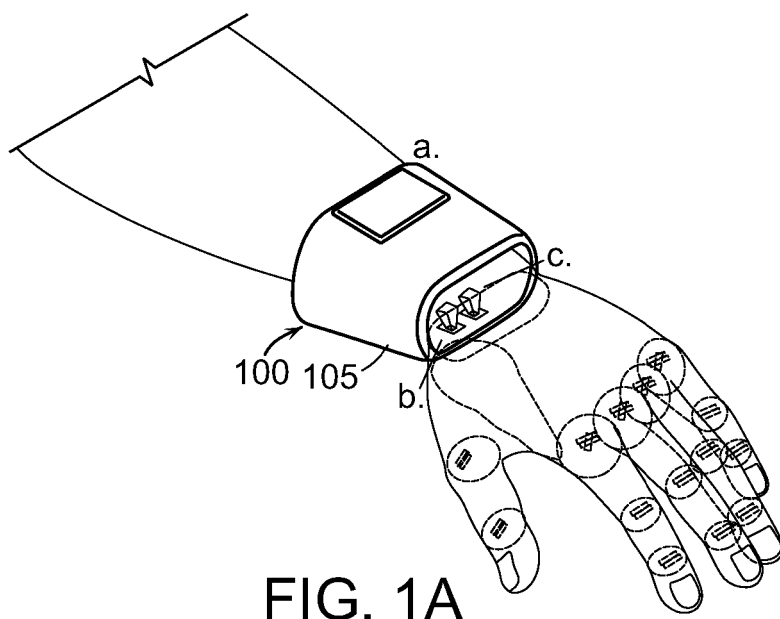
8. Tragbare Vorrichtung nach Anspruch 7, wobei die sensorische Rückkopplung mindestens ein Element aus der Gruppe ist, die aus kutaner Rückkopplung und propriozeptiver Rückkopplung besteht.

9. Tragbare Vorrichtung nach Anspruch 8, wobei der mindestens eine Sensor aus der Gruppe ausgewählt ist, die aus einem Beschleunigungsmesser, einem Positionssensor, einem Drehmomentsensor und einem Gyroskop besteht.

10. Tragbare Vorrichtung nach Anspruch 1, wobei die Steuerung mindestens ein Element aus der Gruppe umfasst, die aus einer reflexiven Steuerung, einer zustandsbasierten Steuerung und einer Mustererkennungssteuerung besteht.

Revendications

1. Dispositif pouvant être porté (100 ; 200 ; 300 ; 400 ; 500 ; 600) pour la commande moteur optogénétique et la restauration de la sensation chez un mammifère, comprenant :
 - a) un support pouvant être porté (105 ; 205 ; 305 ; 405 ; 505 ; 605) configuré pour être positionné à une surface de peau et à proximité d'au moins un nerf périphérique du mammifère ;
 - b) une source d'énergie ('a') au niveau du support pouvant être porté ;
 - c) un dispositif de commande situé sur le support pouvant être porté et en communication électrique avec la source d'énergie ; et
 - d) une source de lumière transdermique ('b') au niveau du support pouvant être porté et couplée au dispositif de commande, le dispositif de commande étant configuré pour utiliser un retour d'information en boucle fermée provenant d'au moins un capteur en communication avec le dispositif de commande pour piloter la source de lumière afin de diriger la lumière à partir du support pouvant être porté et vers au moins un nerf périphérique du mammifère lorsqu'il porte le support, la source lumineuse émettant de la lumière à une longueur d'onde requise pour qu'une opsine spécifique réponde à l'éclairage, l'opsine spécifique étant d'un type qui est fonctionnellement exprimé par un nerf modifié par optogénétique, le dispositif de commande commandant au moins la fréquence, la puissance et le rapport cyclique de la lumière dirigée pour induire une contraction musculaire pour la commande moteur ou pour fournir une stimulation des fibres sensorielles pour restaurer la sensation.
2. Dispositif pouvant être porté selon la revendication 1, le support pouvant être porté étant une sangle.
3. Dispositif pouvant être porté selon la revendication 2, la sangle étant un élément choisi dans le groupe constitué d'une sangle de poignet, d'une sangle de genou, d'un collier, d'un bandeau, d'une sangle de cheville, d'une sangle de jambe, d'une sangle d'estomac et d'une sangle de bras.
4. Dispositif pouvant être porté selon la revendication 1, le support pouvant être porté étant un patch adhésif.
5. Dispositif pouvant être porté selon l'une quelconque des revendications 1 à 4, la source de lumière transdermique comprenant au moins un élément choisi dans le groupe constitué d'une diode électroluminescente (LED), d'un laser à l'état solide pompé par diode (DPSS), d'un laser à diode, d'un laser à l'état solide, d'un laser à cavité verticale émettant par la surface (VCSEL), et d'une diode laser à émission latérale (EELD).
6. Dispositif pouvant être porté selon l'une quelconque des revendications 1 à 4, la source de lumière étant d'un type qui émet une longueur d'onde dans une plage comprise entre environ 300 nm et environ 1100 nm.
7. Dispositif pouvant être porté selon la revendication 1, comprenant en outre l'au moins un capteur en communication avec le dispositif de commande, l'au moins un capteur fournissant un retour sensoriel au dispositif de commande qui commande la source de lumière pour ainsi stimuler sélectivement l'au moins un nerf.
8. Dispositif pouvant être porté selon la revendication 7, le retour sensoriel étant au moins un élément du groupe constitué du retour cutané et du retour proprioceptif.
9. Dispositif pouvant être porté selon la revendication 8, l'au moins un capteur étant choisi dans le groupe constitué d'un accéléromètre, d'un capteur de position, d'un capteur de couple et d'un gyroscope.
10. Dispositif pouvant être porté selon la revendication 1, le dispositif de commande comprenant au moins un élément du groupe constitué d'un dispositif de commande réflexif, d'un dispositif de commande basé sur l'état, et d'un dispositif de commande de reconnaissance de modèle.



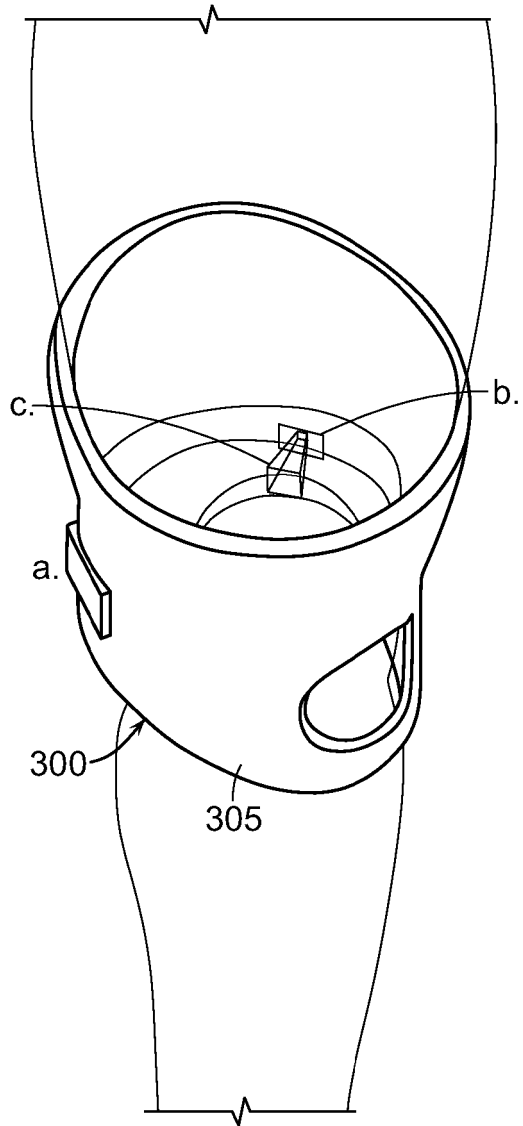


FIG. 3A

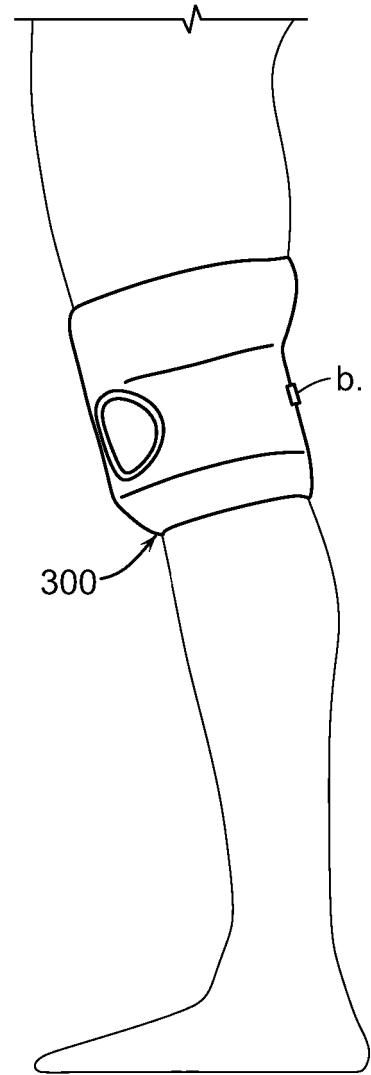


FIG. 3B

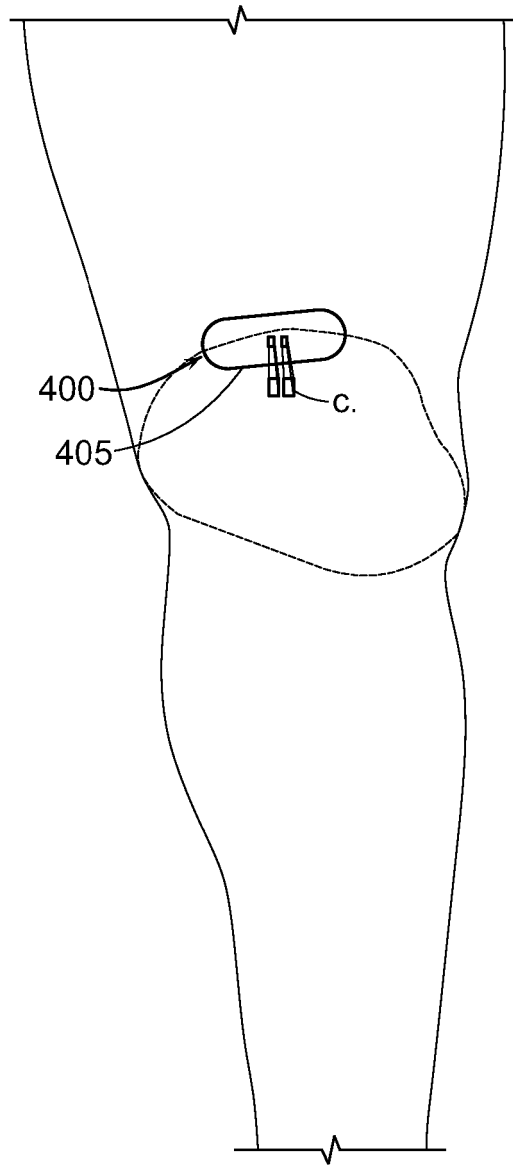


FIG. 4A

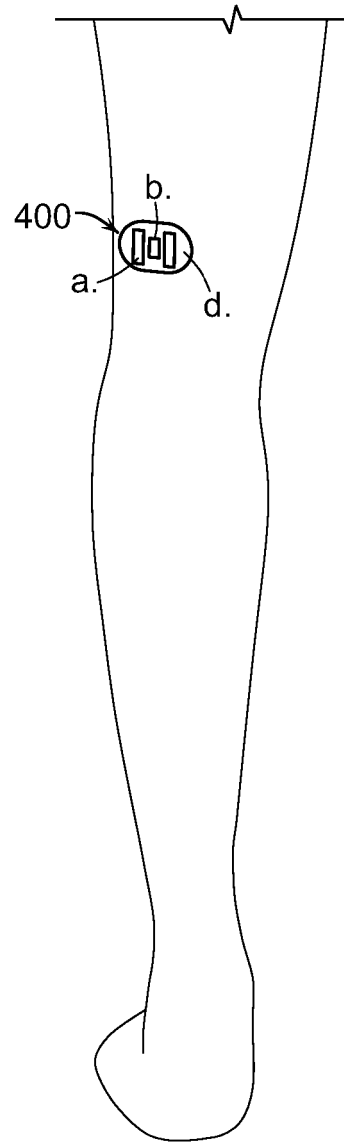


FIG. 4B

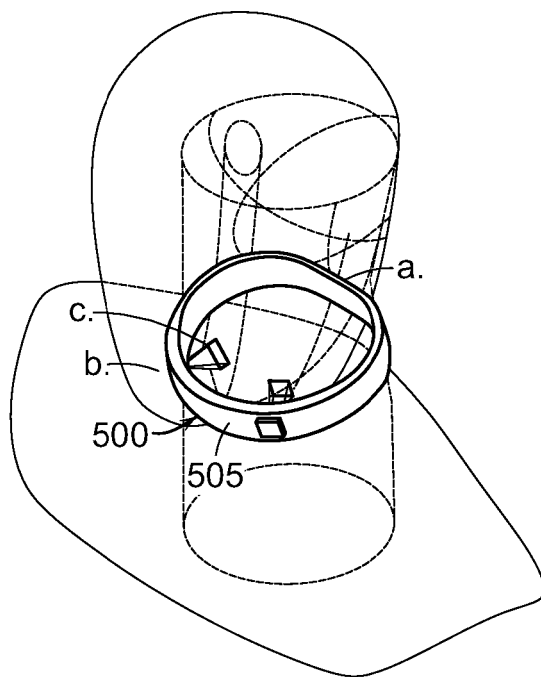


FIG. 5A

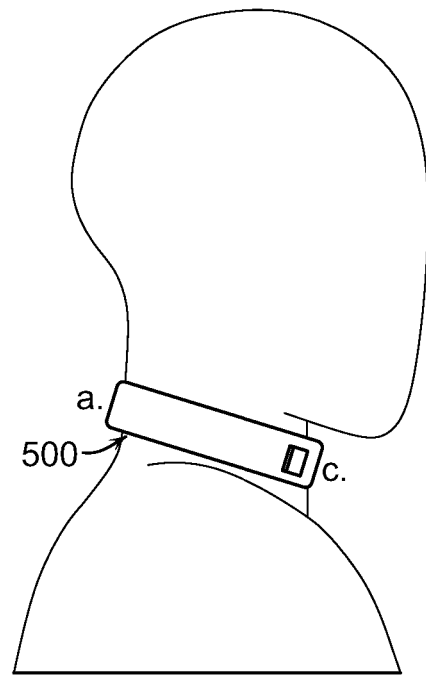


FIG. 5B

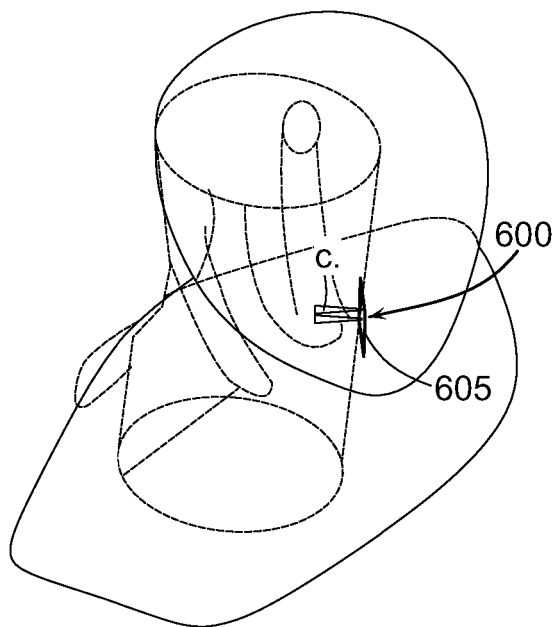


FIG. 6A

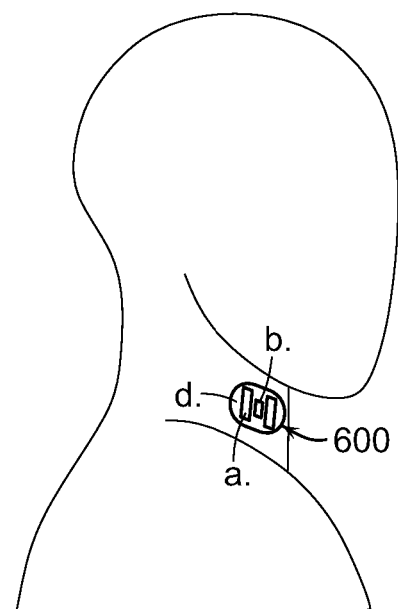


FIG. 6B

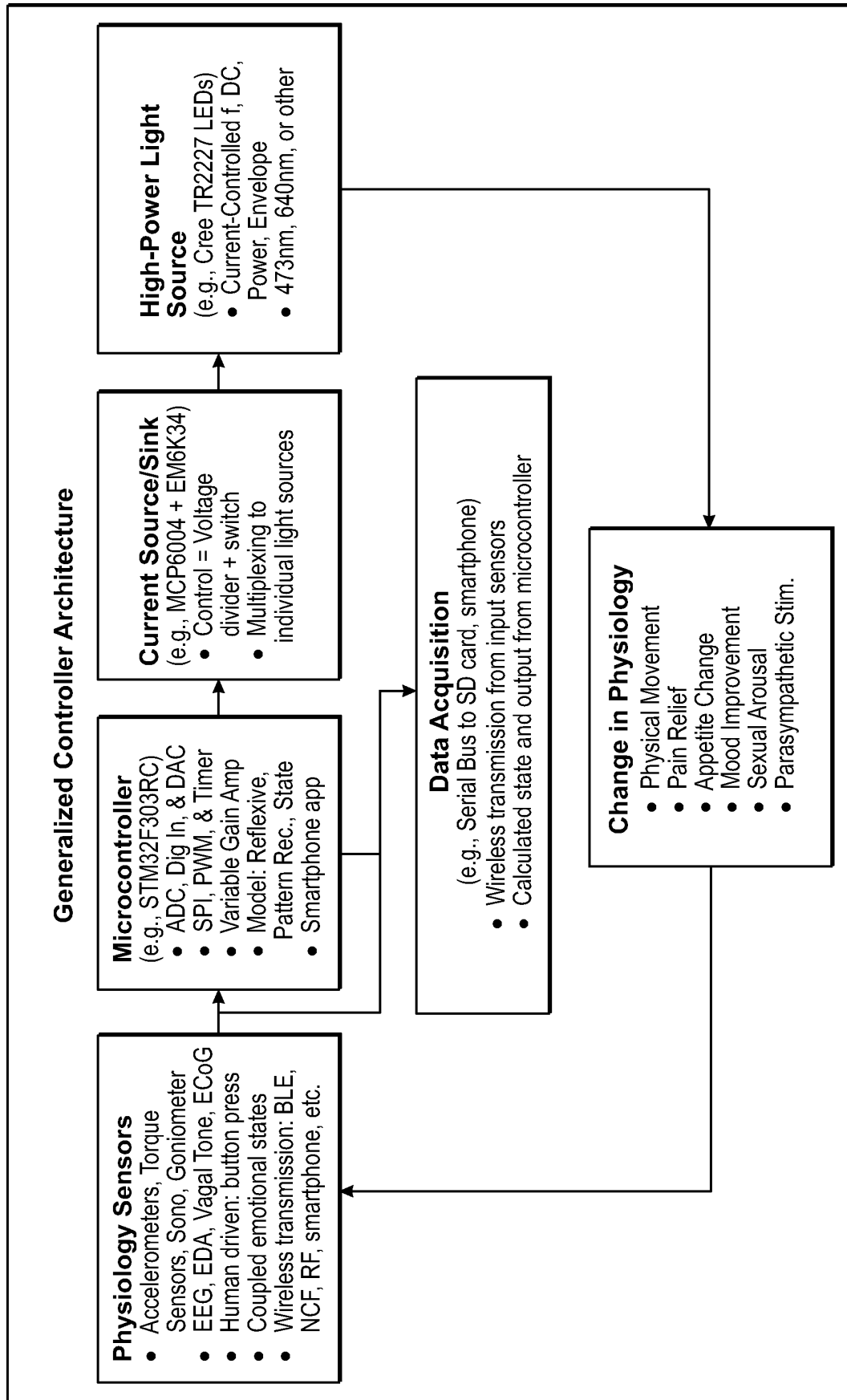


FIG. 7

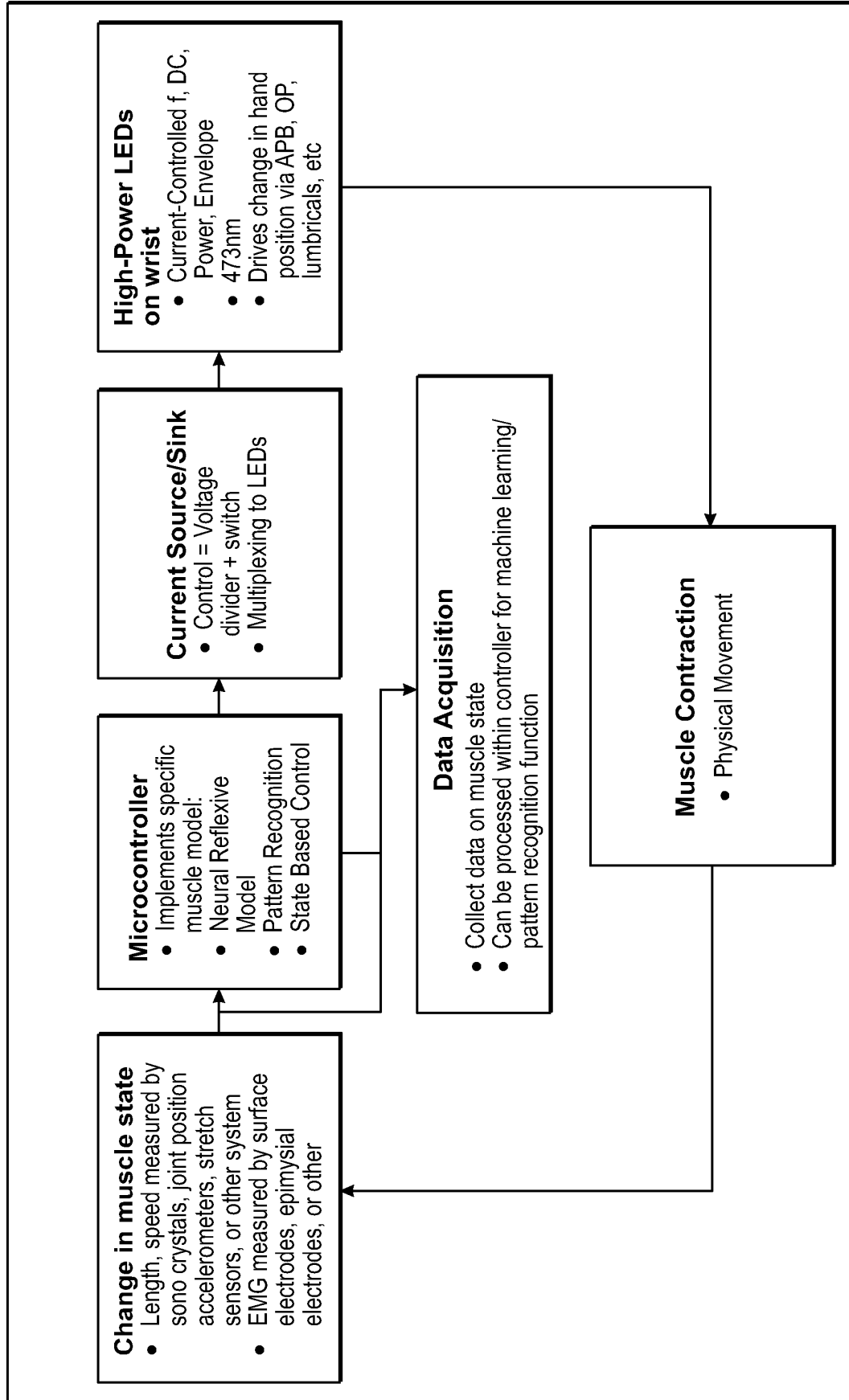


FIG. 8

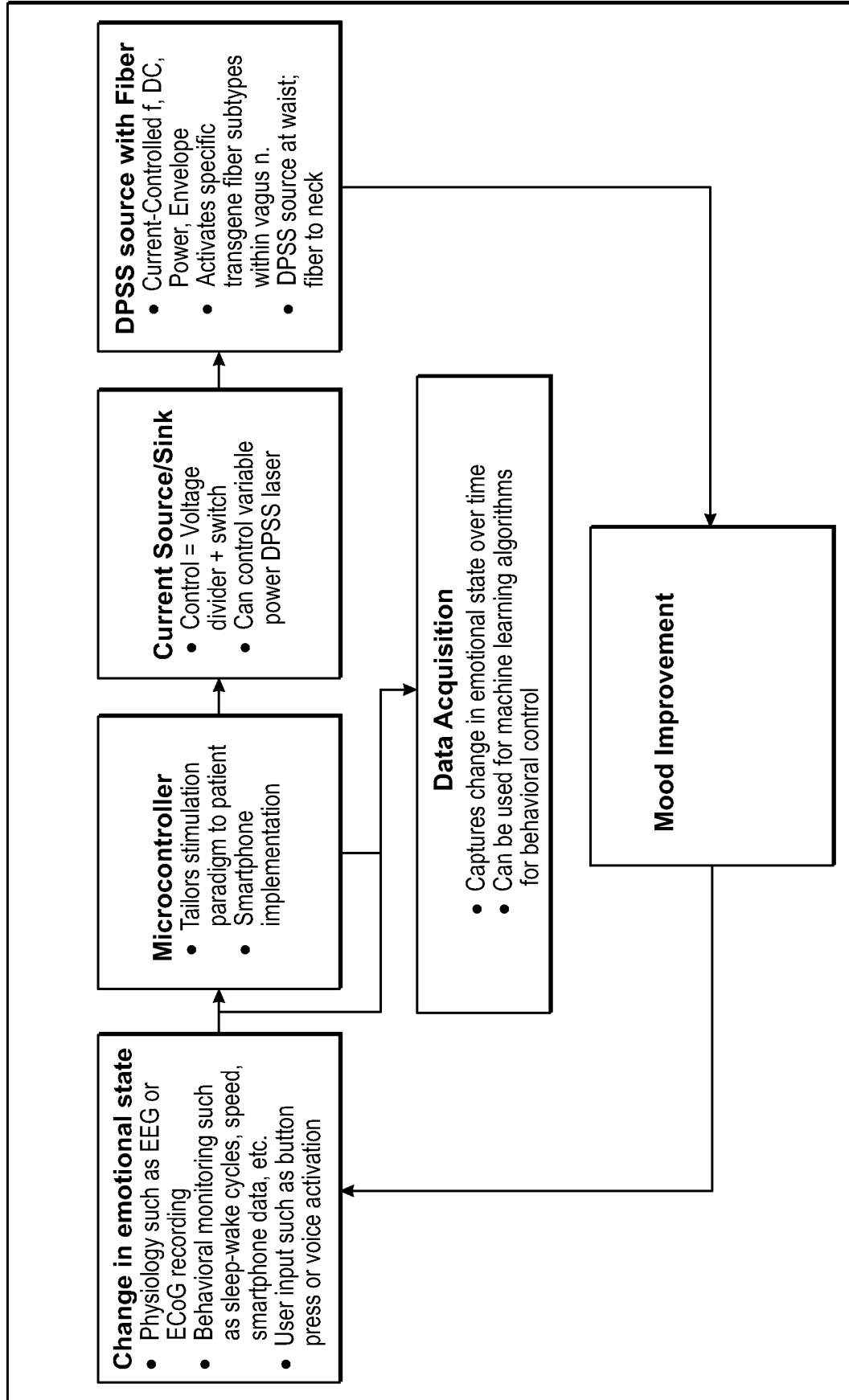


FIG. 9

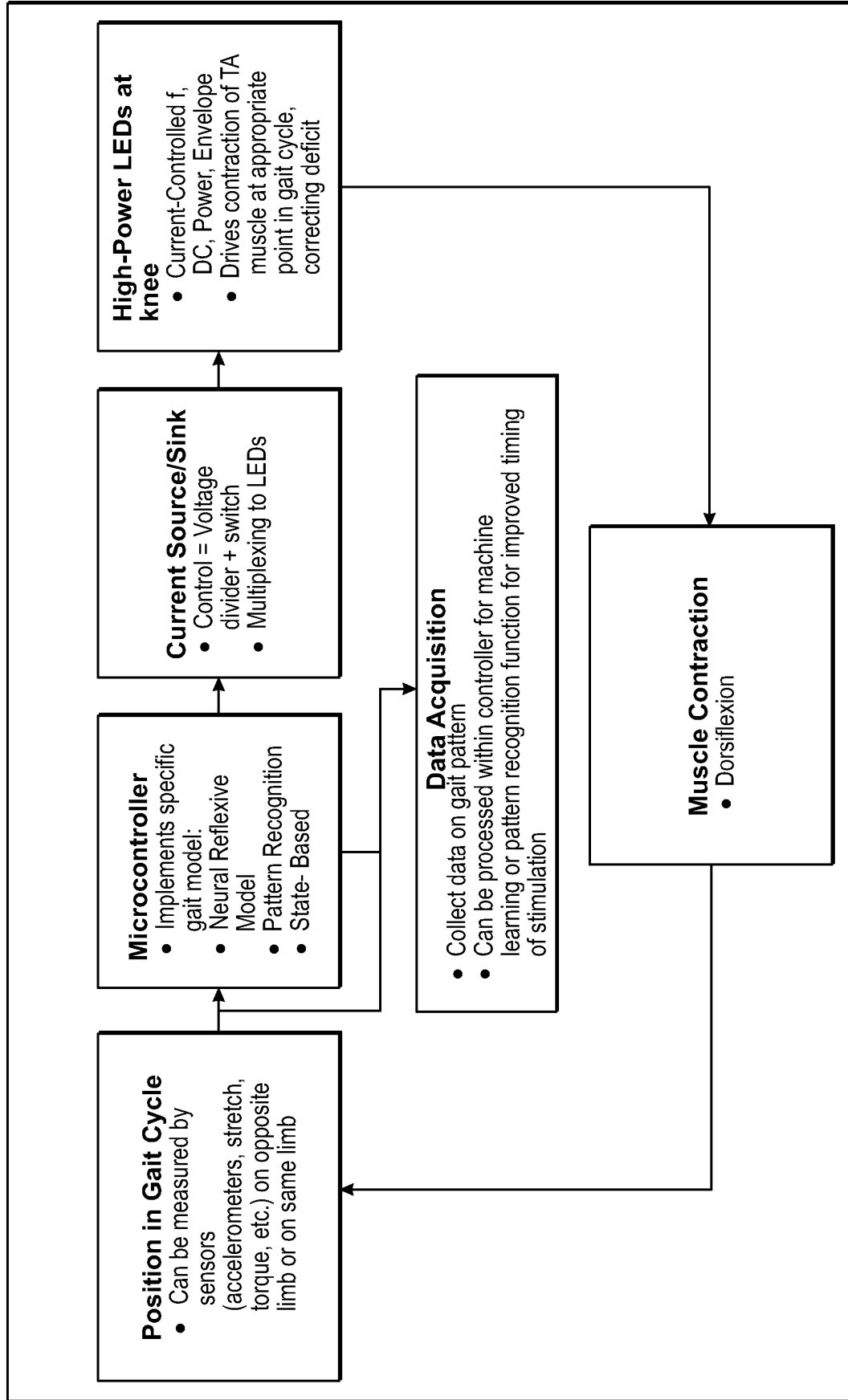


FIG. 10

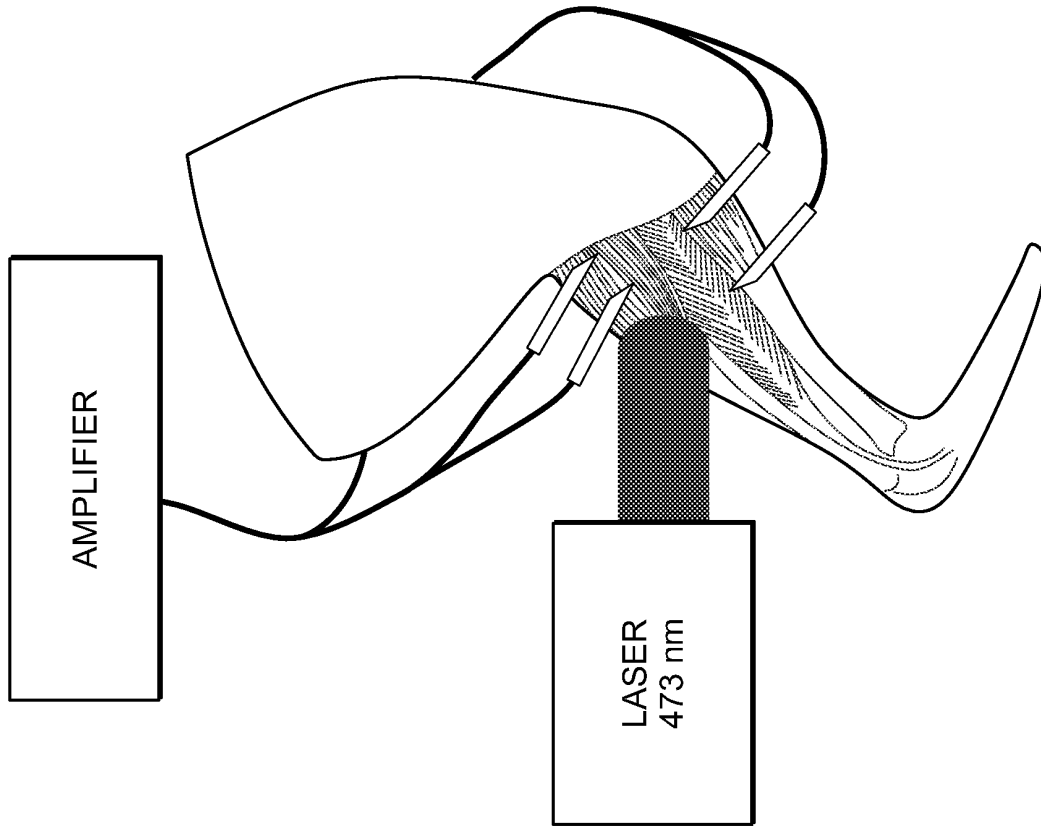


FIG. 12

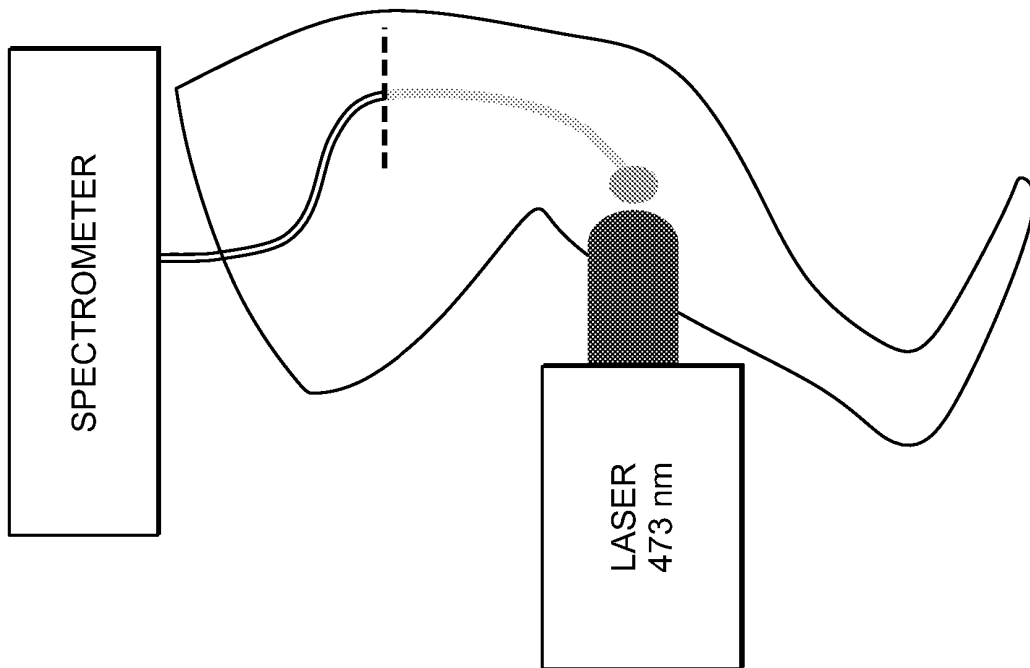


FIG. 11

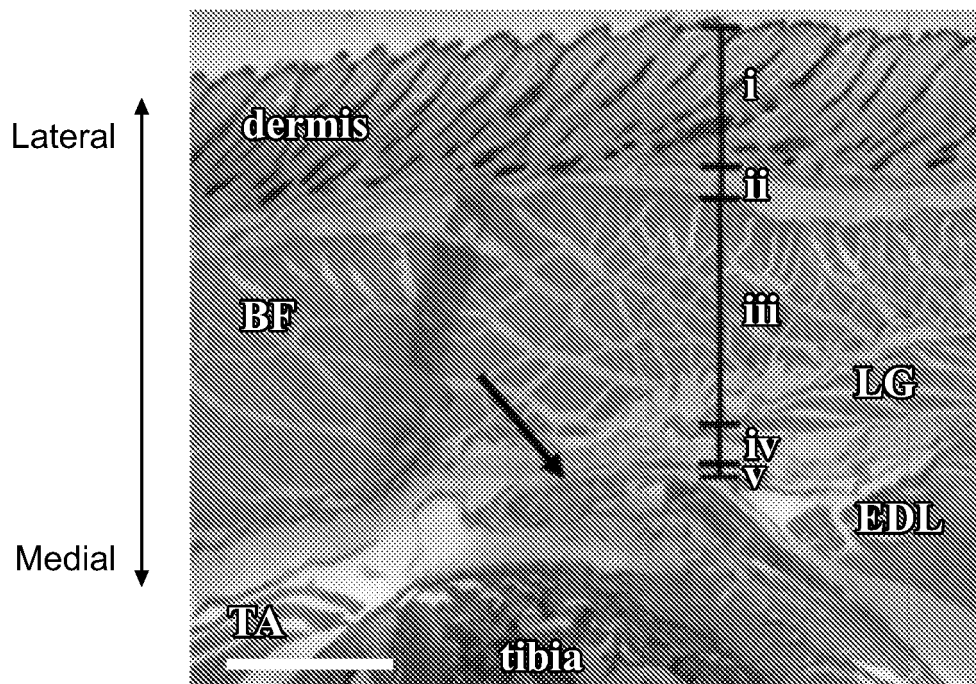


FIG. 13

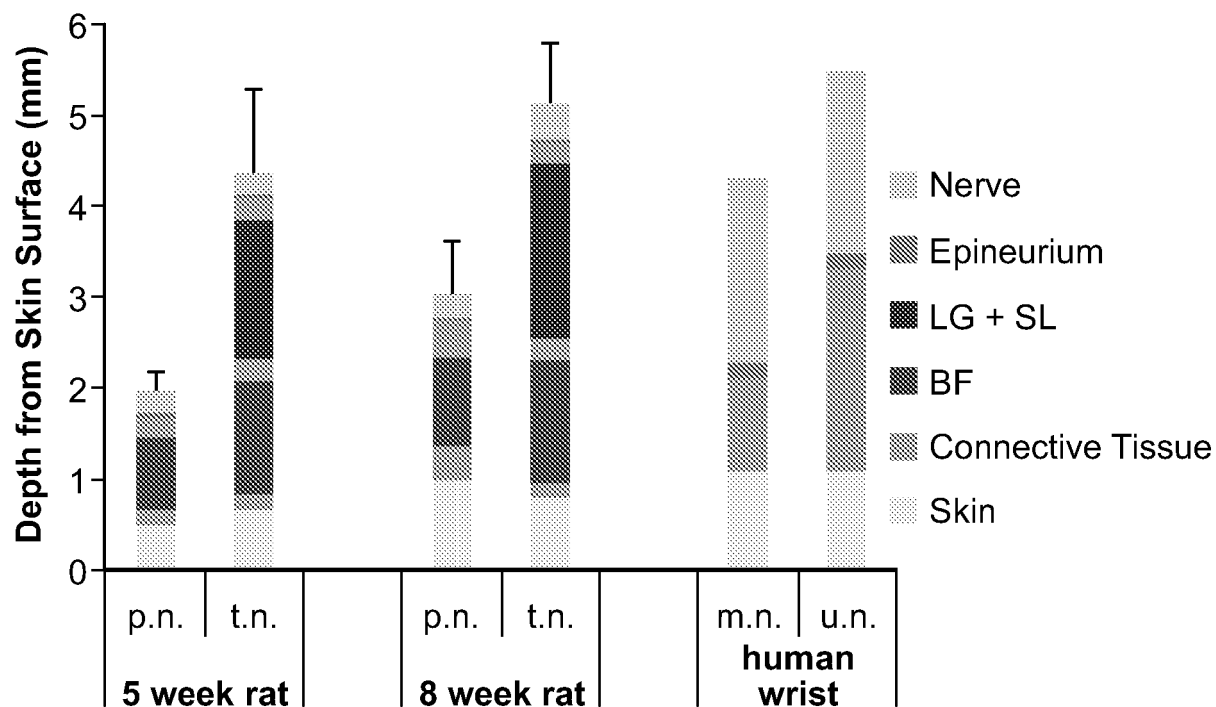


FIG. 14

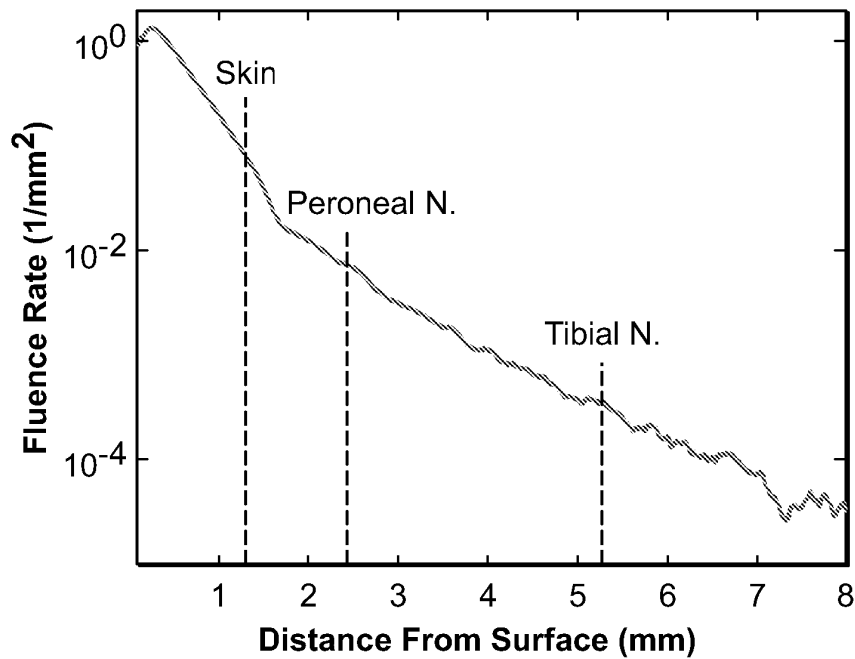


FIG. 15

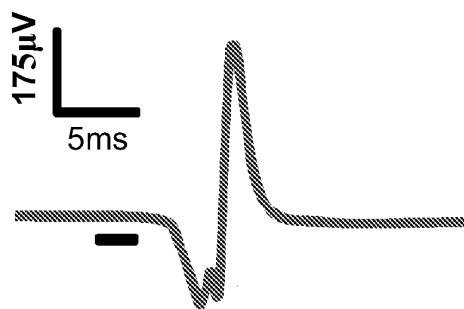


FIG. 16

Inj Age	vp	3 wk	5 wk	8 wk
Adult: 8 week	2E+ 11			
	7E+ 11			
	3E+ 12			
	5E+ 12			
	5E+ 12			
Neonate: P2	3E+ 10			
	3E+ 10			
	3E+ 10			
	3E+ 10			
	3E+ 10			
Neonate: P2 & 2 week	1E+ 12			
	1E+ 12			
	1E+ 12			
	1E+ 12			
	1E+ 12			

transdermal 

direct on nerve only 

no response 

did not assess 

FIG. 17

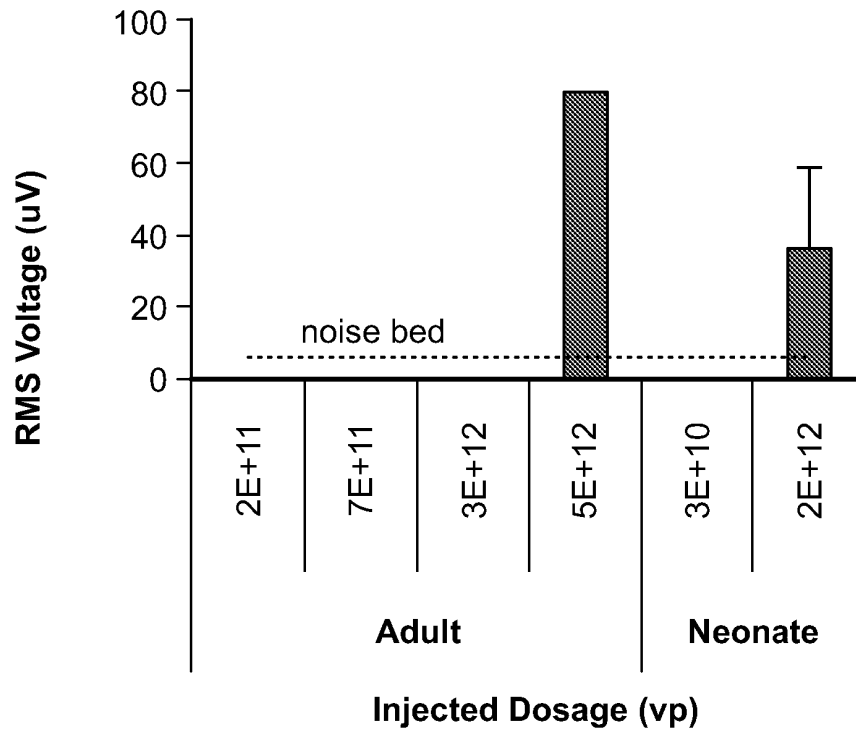


FIG. 18

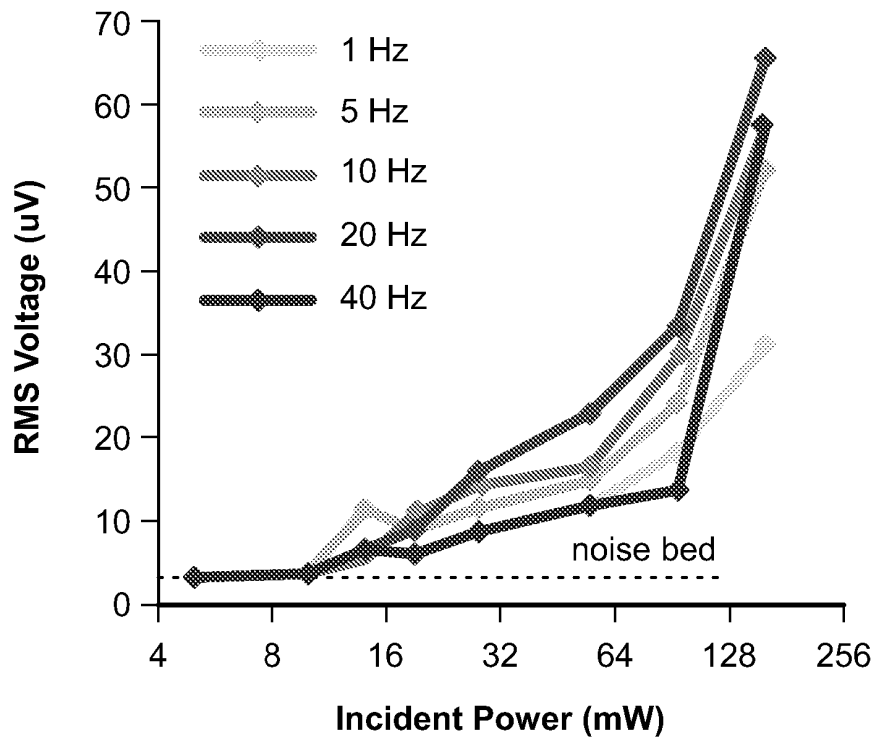


FIG. 19

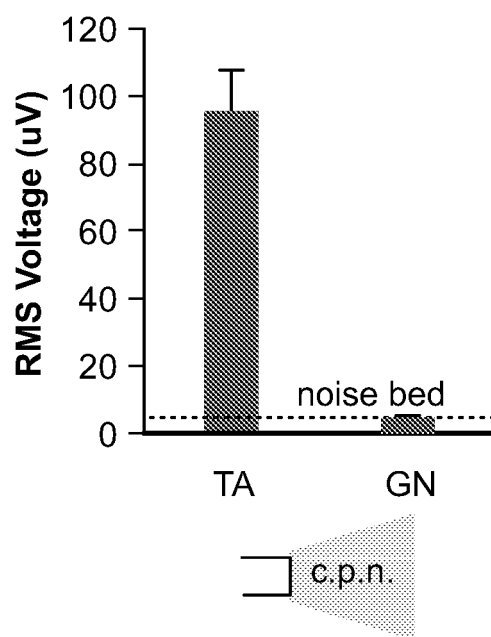


FIG. 20

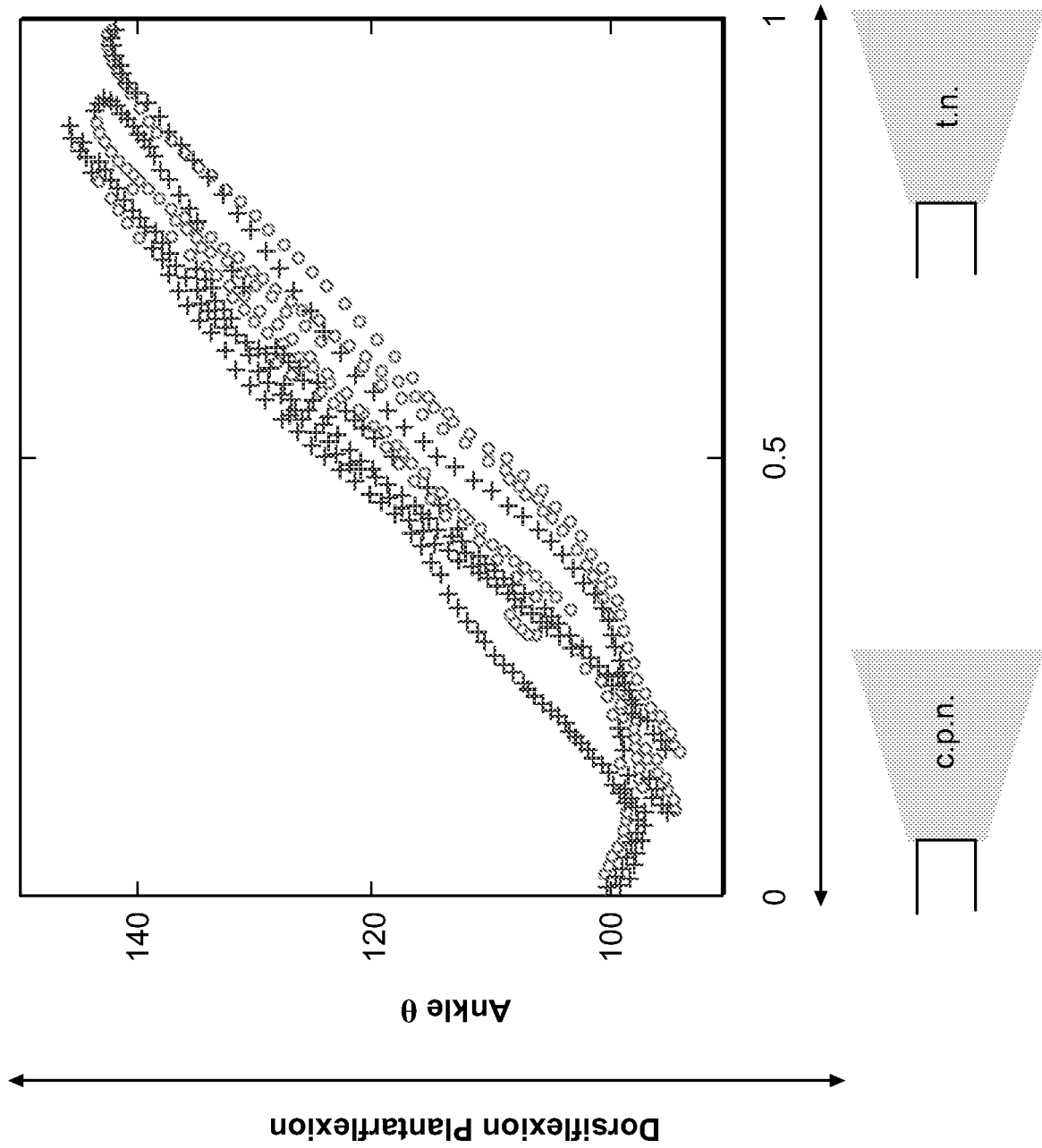


FIG. 21

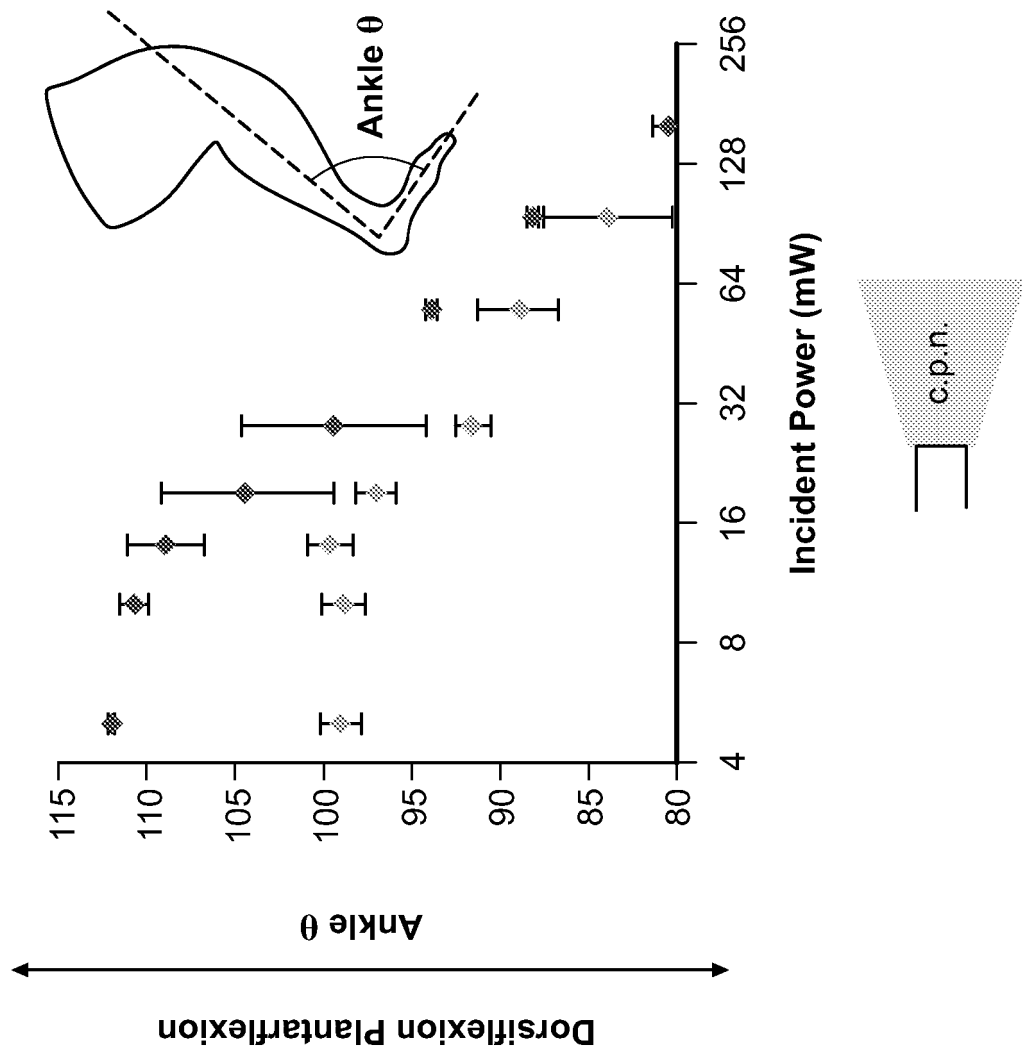


FIG. 22

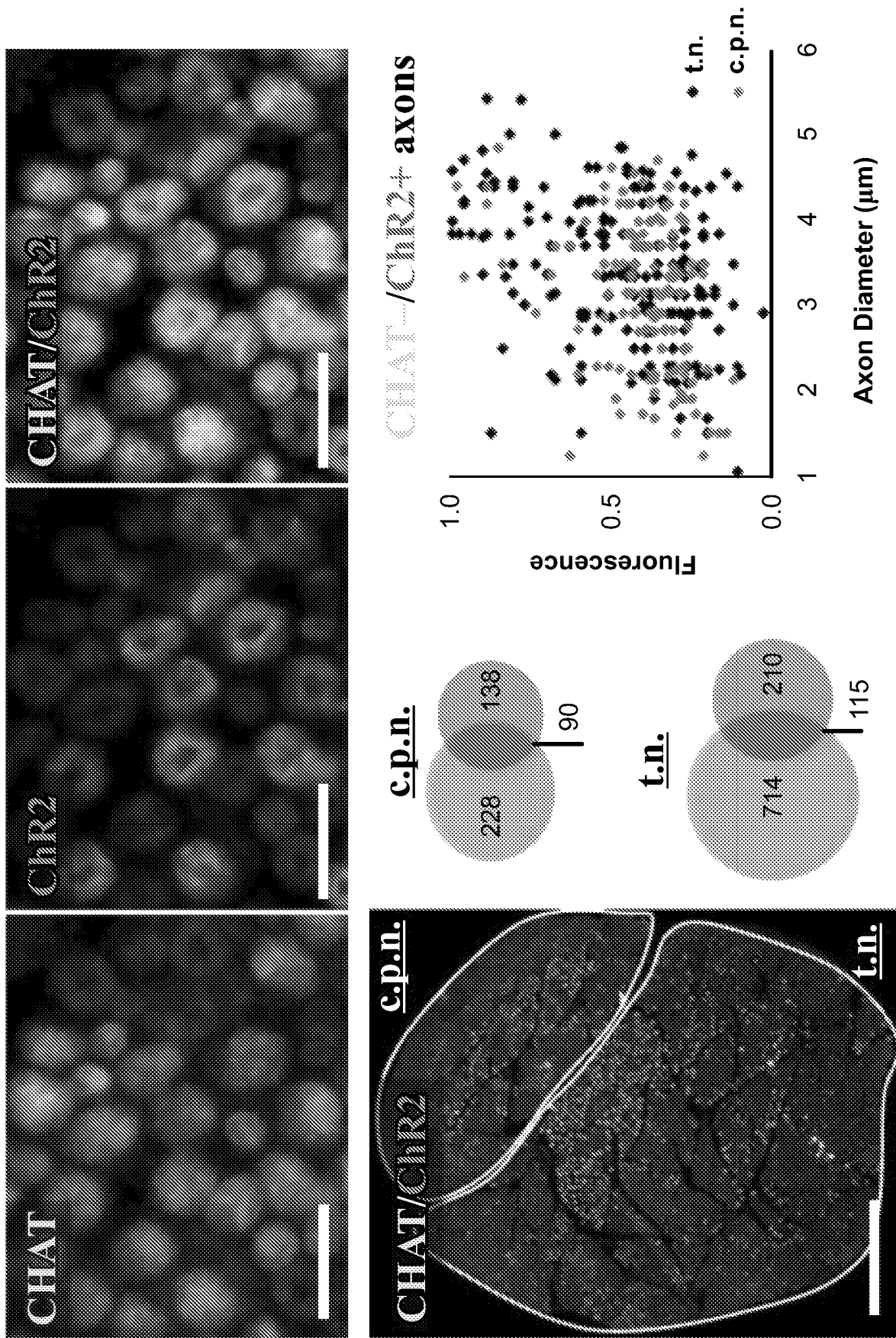


FIG. 23

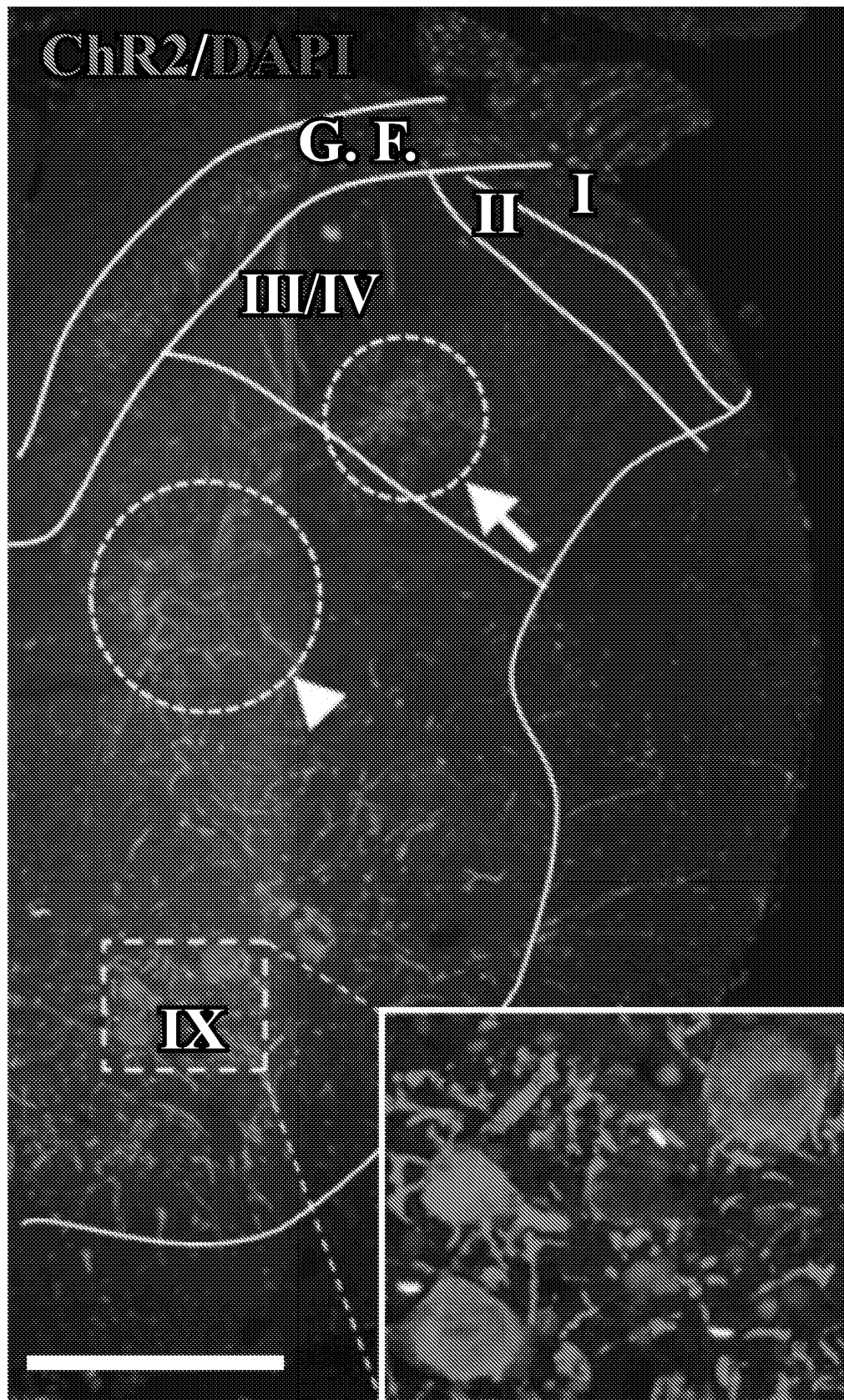


FIG. 24

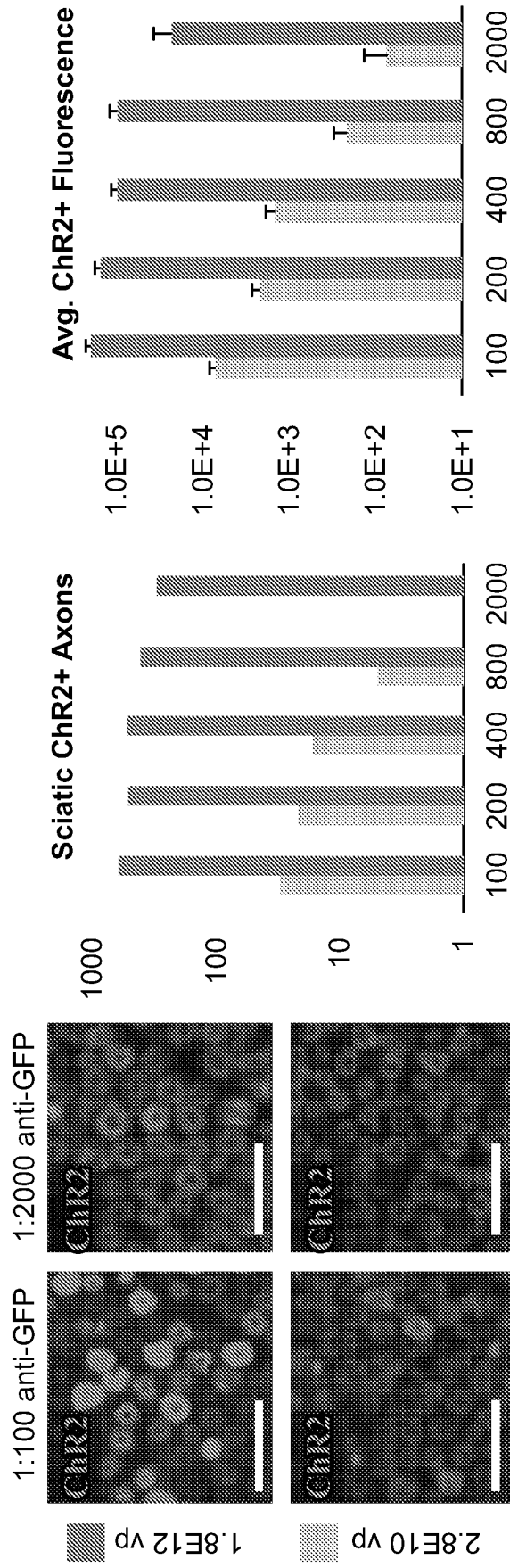


FIG. 25

REFERENCES CITED IN THE DESCRIPTION

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